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JOHN HOMANS LECTURE*

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I HOPE that you will pardon a pride that is so justly mine in having been chosen to give the first John Homans Lecture. This pride is in nowise lessened, but is in fact enhanced, by a realization that I am here not on my own account but as the representative of a large group of surgeons who for many years have studied at the feet of this master and have "learned his great language; caught his clear accents."

The name of John Homans is one of the traditions of which Boston is made. About fifty years before the British colonies in the New World declared their independence, a sea captain of that name brought to Boston the first microscope owned by Harvard. This may have been the initial influence that has shown itself through five successive generations in which a John Homans has studied medicine and practiced it in Boston. A tradition such as this surely nurtures a family pride, which in turn endows its members with sureness of accomplishment yet fosters humbleness toward personal achievement.

This medical dynasty, which has served its country in every major war, originated with a regimental surgeon of the Continental Army who may possibly have been distinguished for selling neither rum nor furloughs. This Revolutionary War surgeon witnessed the Battle of Bunker Hill, spent a winter at Valley Forge and took part in such major campaigns as those of Harlem, White Plains and Saratoga. His grandson was a surgeon for both the Army and the Navy in the Civil War, and his great-grandson, the John Homans we are honoring today, served in France in World War I. The fifth John Homans graduated from Harvard Medical School in 1941 and saw service in a field hospital in the Pacific area during World War II.

As an undergraduate at Harvard from 1895 to 1899, Dr. Homans was socially inclined and was an undistinguished if persistent athlete, yet he graduated *cum laude*. He led his class at Harvard Medical School, from which he graduated in 1903, and received an appointment as surgical intern or "house pupil" at the Massachusetts General Hospital, with which he had already become acquainted as a student "striker," an experience he describes in some reminiscences of his medical training as "rather a nightmare."

After his service as house officer at the Massachusetts General Hospital, he became assistant to Maurice Richardson, Moseley Professor of Surgery at Harvard and the most prominent surgeon of his time. This association proved a happy and inspiring one and was undoubtedly a great and lasting influence. Dr. Richardson had reason to believe that his successor was likely to be Dr. Cushing, then at Johns Hopkins University School of Medicine, so off to Baltimore with a letter to Dr. Cushing he sent Dr. Homans, who spent the ensuing year in the Hunterian Laboratory.

The Peter Bent Brigham Hospital opened in 1912, with Dr. Cushing as surgeon-in-chief. Much has been written and more said about Dr. Cushing's ability to pick men. His first opportunity came with the organization of this venture in teaching and practice; for his two principal associates he chose John Homans and David Cheever. Born and bred in the Boston tradition, both were sons of Harvard professors — both with sparkling personalities but each a gem of different cut. Although a graduate of Harvard Medical School, Cushing was generally regarded as a Yale man, born in the Middle West, with the added stigma that his forebears sprang from Connecticut and not from Massachusetts. These new associates, — and Dr. Cushing, for that matter, — were in no easy spot. Cushing's was an overpowering personality, and it was due to the wise counsel and sound teaching of his associates that general surgery as well as neurosurgery played an important part in the development of this upstart institution. How wisely Cushing chose, I leave to you and to history.

In its first years, the Brigham's clinical load was not heavy; consequently the papers published by Dr. Homans were largely of an experimental nature, notably three concerning the pancreas in relation to carbohydrate metabolism and diabetes. He was close to insulin, but that's another story. With the

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Brigham's expanding service, the operating and teaching load became heavier and heavier, and the laboratory lost to the clinic a valuable investigator.

During 1918 and 1919, Dr. Homans served in the Army Medical Corps, with the rank of major, as chief of an operating team in various evacuation hospitals.

After his return to the Brigham, he published a long series of papers on general surgery, with particular attention to circulatory disturbances. The academic year 1936–1937 was spent at Yale as professor of surgery *pro tempore* for Samuel Harvey, who was on leave. There he made the imprint that might be expected. For a leading professor of Harvard to become, within so short a time, one of Yale's best remembered and most popular teachers mirrors the personality of the man (or perhaps it merely reflects the native discrimination of Yale men). Harvard and the Brigham claimed him again until 1946, when he retired as clinical professor of surgery, emeritus, of Harvard Medical School and surgeon emeritus of the Peter Bent Brigham Hospital.

This is but an all too brief excursion into the professional life of a many-sided man who has spanned the scene from Cy Young to Ted Williams.

A survey of Dr. Homans' bibliography reveals a total of some hundred scientific papers. Included in the list are two books. The first of these, *A Textbook of Surgery*, appeared in 1931. Widely acclaimed and immediately popular, it required the difficult task of many revisions. Unwilling to nurse this success, he wrote the monograph *Circulatory Diseases of the Extremities*, which appeared in 1939 and has taken its place as a classic in the field of vascular disorders.

When the *Textbook* was just off the press, it was reviewed for the *New England Journal of Medicine* by Dr. Cushing, who, as was his wont, offered his praise along with frank criticism. Here Dr. Cushing pointed out that although it had many contributors the book was really Dr. Homans'. He set his estimate on the work with these words:

> For here is a book about surgery to *read*, the like of which to the writer's knowledge has not been produced in modern times. . .The Irishism that Osler's "Medicine" was the best existent work written on *surgery* has often been repeated. It was a book, in other words, that *the surgeon* could not well be without. . .but now we have a work on surgery which *the physician* cannot well be without, for sanely and picturesquely it gives just the sort of information about his colleagues' problems and point of view that he needs to have at hand. And so far as concerns the undergraduate student for whom the work is primarily intended, this is a book, like Osler's, which is as easy reading as a novel. . . .

To one who had sent him a commentary on the first edition, Dr. Homans wrote:

> Many thanks for letting me see the review of my textbook. It is the first I have seen. Of course, you are so complimentary that I blush rather freely. The difficulty about the book as I see it is that all of my old friends and a number of highbrows seem to be pleased with it. What I want to hear is something from one who has a natural inclination to think that I am a skunk and who represents, as it were, the great heart of the people; the people, indeed, who have to pay for the book. Nevertheless, I thank you.

The historical introductions to the chapters are a natural way of leading the student into the subjects, although Dr. Homans in the preface calls some of the matter "merely diverting" and the student finds there many humorous comments that lighten the load of learning. In an early chapter there is mention of bichloride of mercury as an antiseptic, and the author states, tongue in cheek: "Its chief use is as a solution in which operator and assistants may rinse their gloved hands during an operation. Many a surgeon has pulled himself together in a difficult situation while so doing."

A medical student once asked me in all seriousness just what was meant by that statement. Believing myself inadequate for an explanation, I referred the question to the author. He replied that I might have suggested to the student that "the next time he played in a poker game, he might pull himself out of a tight place by walking around the chair; on the other hand, it might be better to soak his head in a bowl of iodine."

Of mercurochrome he said: "It is a good antiseptic for minor wounds and stains the parts a bright red." A historical paragraph on cancer of the stomach reads: "Matthew Baillie, who wrote the first really systematic book on pathology (1793), said of cancer of the stomach that it was more common in men than in women. . . . He was familiar with the varied appearances of cancer, and believed it usually began near the pylorus." To this Dr. Homans adds: "Not much more is known of the disease today."

Written primarily for medical students, the book was naturally most appreciated by teachers. It is a work that shows tremendous erudition and scholarly research, and a clarity such that "he that runs may read." It is not surprising that in these twenty years it has gone through six editions and nine printings and has been used in as many as sixty-five medical schools as a selected text in a single year.

Among his more important contributions to the field of vascular surgery is his description of bland thrombosis causing pulmonary embolism. This paper, presented in 1934 (in the *New England Journal of Medicine*), marks the beginning of our knowledge of the true nature of this disease and its clear differentiation from thrombophlebitis. Here the signs and symptoms illustrated by four cases are clearly and succinctly set out and the treatment by femoral-vein ligation advocated. Note the clearness:

> A local, deep thrombosis in the lower leg begins with a variable but, on the whole, a moderate amount of discomfort in the calf, swelling at the ankle, and blueness of the foot; signs which are rather promptly made to disappear upon rest in bed, but which recur over and over

again upon attempting the use of the leg. It is hard to believe that, as a result of elevation for only a day or two, the leg, actually the seat of an extensive deep thrombosis, can take on so nearly, or completely, normal an appearance. Yet autopsy in the fatal cases has shown a remarkable widespread, persistent thrombosis in the great vessels among the muscles of the calf. In each case, the femoral vein was actually obstructed and the cause of the fatality was the detachment of a considerable fragment of an enormously long, insecure thrombus which had been waving, as it were, in the current.

And again:

Thrombophlebitis of the "milk-leg" type, that is, phlegmasia alba dolens, is primarily a pelvic process, though the thrombosis may extend for a long distance peripherally. Explorations by the writer have shown that in many instances there is an active exudative reaction about the external iliac artery and vein (the common iliac or even the vena cava in some cases). The great vein is solidly obstructed by a firm thrombus. The whole leg, not just the lower portion, is swollen. In some instances, there is evidence of arterial spasm resulting in some degree of ischemia. In all cases, going to bed has little effect upon the disease, the swelling persisting in even the mildest cases for a week or ten days and occasionally for many months. There is always tenderness over the deep vessels at the groin and over the femoral canal. Embolism, considering the frequency of the disease, is uncommon, a matter which may be related to what seems to me to be the usual source of the process, that is, an inflammatory reaction within the arteriovenous sheath.

This ranks as one of the classic descriptions of a common and hitherto poorly understood disease.

In a letter to one of his pupils who had written him concerning his own attack of bland thrombosis, he wrote:

As for Homans' much maligned sign, it was in the cases like yours that I first experienced it without attributing any tremendous importance to it. In fact, I was rather overcome that the sign was given my name. Of course pain had very little to do with it. The main point was the muscular tension due to the irritability brought about by the process.

One of the most outstanding characteristics of Dr. Homans' writing, — and of his speech, — is his way of stating things with a simplicity that makes a lasting impression. In his monograph *Circulatory Diseases of the Extremities* he shows how easily a diagnosis may be arrived at through the history and a physical examination with simple tests such as examination of the peripheral pulses, the temperature of the extremity as felt with the hand, and color changes.

In discussing tests for vasodilatation, there is no talk of constant-temperature rooms, oscillometers, plethysmographs and thermocouples but rather of alcohol: "A stiff drink of whiskey or any strong liquor is, except for the corruption of the individual, an admirably simple and practical method of testing the ability of the vascular bed to dilate." Note that the amount of whiskey was not prescribed in cubic centimeters; anyone should know what a "stiff drink" is.

As a matter of fact, although Dr. Homans knows well, and frequently mentions, the value of certain instruments of precision, he rarely uses any such aids in making the examination but only the senses that God gave him and a recollection of past experiences.

His great contribution to the field of vascular surgery lies not only in the originality of his observations but in his willingness to share his knowledge with all who would listen and in his ability to stimulate others. He has never been dogmatic about methods of treatment, realizing the changes that time brings about. Most men who record an original observation and propose a method of treatment usually refuse to modify their beliefs. For many years an advocate of femoral-vein ligation in treating bland thrombosis, he has willingly accepted and practiced anticoagulant therapy.

Possessor of what Dr. Burt Wolbach once described as an "afflicting conscience," Dr. Homans has many times illustrated the truth of that statement by acts such as his refusal to accept an honorarium offered for a lecture given while he was visiting a former pupil because, in his own words, "I cannot bear to have made a profit, so to speak, out of my visit. . .that is, in money." His outstanding honesty has often led to his personal disparagement. On one occasion I asked him if he had ever accidentally cut the common duct. He replied: "I am probably the only man alive who has cut the common duct twice in the same patient, and moreover, in the same operation."

There is an envy-evoking freedom in his sense of humor that is as unpredictable as Boston's weather and as versatile as its subways that run overhead and its elevated railways that run underground. But as Emerson said, "A foolish consistency is the hobgoblin of little minds. . . ." An endless variety of stories, — and Dr. Homans is a raconteur of rare ability, — usually illustrates the subject of his conversations. These often concern personal experiences or those of family, friends and associates, although, I might add, there are a few other stories that are good for retelling but less adaptable to print.

A long-lived influence of that seafaring forebear is a love of sailing and salt water, exceeded only, perhaps, by a love of the hunt. Dr. Cheever tells us that "so well known was this passion for shooting, the teaching schedules at the Brigham were arranged to allow for Jack Homans' absence during hunting season." There are other interests and aptitudes — the woodwork, the arboriculture, bridge, conversation, *Sängerfests* and even the mixing of a good cocktail. I know from experience that his improvisations in that respect during the "noble experiment" were perfectly marvelous.

I first met Dr. Homans when I was filled with youthful romantic illusions. He quickly knocked them out. I found him as salty as the Sacred Cod — a salt that has never lost its savor. Here was a man to be trusted immediately. His criticism has rarely been gentle but has always been truthful — severe,

indeed, but flavored with that saving humor. If he has hurt feelings on occasion it was a thorn without a barb, a candid expression reflecting simplicity of thought and rectitude of soul.

Between us there has been a fellowship not only of our craft but of field and stream and gun, and above all, of men — their successes, foibles, wit and fun.

Little that I have said today is worthy of his illustrious name, and I hope that he will forgive me for displaying in public an affection best honored in private.

EFFECTS OF ACTH ON INDUCED MALARIA IN MAN*

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BOSTON

IN THE course of investigations of the antipyretic action of pituitary adrenocorticotrophic hormone (ACTH),[1] the hormone was given to a patient with syphilis of the central nervous system who was undergoing treatment with induced malaria. It was found that the periodicity of the paroxysms and the height to which the temperature rose were apparently not affected by the hormone but that defervescence was accelerated. Routine studies of the life cycle of the malarial parasites during treatment with ACTH revealed unusually high parasite counts in the blood stream. Similar studies were therefore made on other patients; the data thus obtained indicate that ACTH increases the parasitemia in induced malaria.

MATERIALS AND METHODS

The McCoy strain of *Plasmodium vivax* was used throughout. This strain has been maintained by storage of infected blood in the frozen state and has been passed from patient to patient for many years without intervening passage in arthropods and without apparent change in the severity of the induced disease. All the patients studied in this series showed evidence of active syphilis of the central nervous system and were selected as suitable for malarial therapy by the usual criteria. The recipients received 5.0 cc. of freshly thawed blood intravenously; the temperature, red-cell counts and parasite counts were recorded at frequent intervals until clinical malaria developed. The degree of parasitemia was determined from thin and thick Giemsa-stained smears of the peripheral blood, and erythrocyte counts and counts of the percentage of parasitized erythrocytes were made at least once daily. Rectal temperatures were taken during the paroxysms and during the period of agitation in 1 patient; at all other times oral temperatures were used. Temperatures were recorded every four hours until the patients gave evidence of onset of a paroxysm, whereupon hourly temperatures were taken until the patients became afebrile. Fever units were calculated in the usual manner.[1]

ACTH was given intramuscularly every six hours in saline solution (doses expressed in terms of Armour LA-1A standard). The procedure in all cases was to permit 3 paroxysms to occur and then to begin giving the hormone immediately after the third paroxysm. The hormone was given throughout 2 or 3 paroxysms before it was discontinued. The patient was permitted to have 1 or 2 more paroxysms before the infection was terminated with Thiobismol or quinine.

Three male patients with clinical malaria, thirty, forty-nine and fifty-two years old, respectively, were given ACTH in this manner. The degree of parasitemia was compared with that observed in 7 consecutive control patients treated with the same strain of parasite. The patients received routine hospital diets; although we were aware of the effects of diet on the multiplication of malarial parasites,[2,3] it was not feasible, under the circumstances, to attempt rigid dietary control.

RESULTS

Figures 1 and 2 show the temperature responses in 2 of the patients receiving ACTH. It is seen that in both cases there was a slight but reproducible tendency for the number of fever units developed in each paroxysm to be less during the treatment with ACTH than during the control periods. In the third case the results were the same; hence this case is not described in detail. It is noteworthy that the periodicity of the paroxysms was not at all affected and that temperatures rose to the same height while the hormone was being given as before or after it was administered. The decrease in the number of fever units is due to more rapid defervescence in the presence of ACTH.

The recorded parasite counts are shown in Figure 3, in which the counts, as observed on each of the 3 patients receiving ACTH, are compared with counts observed in 7 consecutive control patients who had induced malaria but were receiving no hormone.

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The control patients comprised 6 males aged fifty-one, forty-nine, forty-eight, forty-two, thirty-six and nine, respectively, and one forty-seven-year-old woman.

The distribution of parasite counts on individual days, as well as the mean parasite counts on any

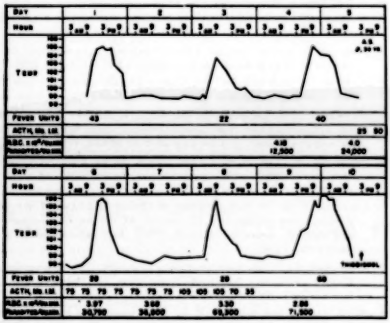

FIGURE 1. *Effect of ACTH on Paroxysmal Fever of Therapeutic Malaria.*

given day, leaves little doubt that the degree of parasitemia was greater in patients receiving ACTH than in controls. The means of the highest counts

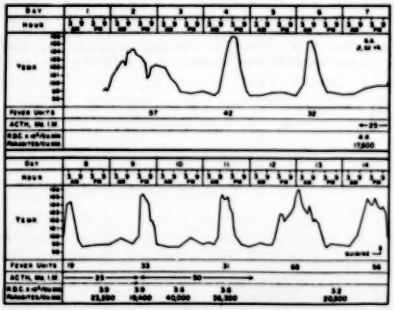

FIGURE 2. *Effect of ACTH in Therapeutic Malaria.*

recorded for the patients receiving ACTH were significantly higher ($P < 0.01$) than the means of the highest counts recorded in control patients.

Two of the patients receiving ACTH showed no untoward reaction and no significant changes in behavior. One patient became agitated, developed a delusional system and finally became so violent that isolation was required. These symptoms cleared about 3 weeks after ACTH was stopped. Prior to treatment and during the earlier paroxysms the patient had showed mild paranoid tendencies, but he had not been agitated and had had no difficulties with other patients.

DISCUSSION

It has been amply demonstrated that cortisone, — and occasionally ACTH, — may depress resistance to infection.[4] The mechanism by which this depression occurs is not clear, but the action of these hormones in inhibiting the inflammatory response and the formation of antibody[5-7] would naturally suggest that such inhibitions account for the depressed resistance. In malaria, however, the acute inflam-

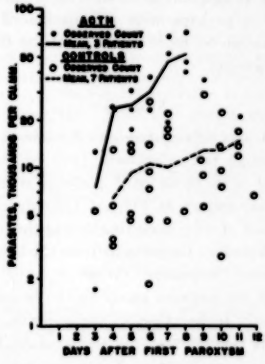

FIGURE 3. *Effect of ACTH on Parasitemia in Therapeutic Malaria.*

matory exudate is not a prominent feature of the host response, and the role of antibodies in immunity, though better defined in avian and simian malaria,[8] is not clear in human malaria.[9] The primary pathologic responses are centered in the reticuloendothelial system.[10] It is possible that ACTH may make available to the parasite a critical nutrient that permits greater multiplication within erythrocytes, or that the hormones interfere with defensive activity and possibly, therefore, with reticuloendothelial function. In apparent contradiction to the latter hypothesis is the observation that adrenalectomized animals show impaired reticuloendothelial activity.[11]

Experimental counterparts to these observations in man have been obtained in experiments with

malaria due to *Plasmodium knowlesi* in monkeys[12] and *Pl. berghei* in rats.[13] In the monkeys, blackwater fever was induced in all experimentally infected animals receiving ACTH.

It is of interest that among the conditions commonly thought to lead to malarial relapse are such factors as intercurrent infection, trauma, exposure to cold, exertion and similar stimuli, although in controlled experiments the imposition of such stresses has not led to malarial relapse.[14] Adrenalin is commonly used to induce parasitemia that is otherwise not demonstrable.[15] The various forms of stimulus that have been considered to predispose to recurrence of malaria, including adrenalin, are adrenocortical activators. It is possible, therefore, that the appearance of parasitemia under stressful circumstances is related to adrenocortical stimulation with subsequent depression of certain host responses, or perhaps with stimulation of parasitic multiplication by more direct effects on the growth of the organism.

Summary

ACTH was administered to 3 patients with induced benign tertian malaria; their responses were compared with those of 7 patients with malaria who did not receive ACTH. ACTH reduced slightly the amount of fever occurring during the paroxysms but did not affect the periodicity or the height of the temperature responses. However, the parasite counts in the patients receiving the hormone were significantly higher than in the controls. The observations suggest that the action of ACTH in reducing resistance to infection may include an effect on components of host resistance not directly related to the acute inflammatory response and probably not directly concerned with antibody production.

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MICROSPOROSIS OF THE SCALP*

Evaluation of a New Therapeutic Agent

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BOSTON

BY COMPARISON with other large cities, Boston has not had the high incidence of tinea capitis prevalent in most of the country.[1, 2] It has, however, experienced a rapidly increasing incidence of infection with the human type of ringworm of the scalp, *Microsporum audouini*, as compared with the correspondingly diminished prevalence of the cat and dog type (zoophilic), *Microsporum canis*. This changing picture is a matter of growing concern because of the already widely recognized greater resistance and longer persistence of infection with the human type, *M. audouini*.

Therefore, any new antifungoid preparation that promises superiority is avidly seized by those who are aware of the seriousness of this problem. The drug under consideraion was supplied to us by the maufacturer with the tentative designation of Ro2-2453; it was more recently named Asterol Dihydrochloride.¶ It is described by Grunberg and others[3] as 2-dimethylamino-6-(beta-diethylaminoethoxy)-benzothiazole dihydrochloride — colorless crystals, readily soluble in water and alcohol. They found it particularly active against the trichophytons and the microsporums. Stritzler, Fishman and Laurens,[4] using 5 per cent ointment and 5 per cent solution in alcohol, report that of 61 children infected with *M. audouini* 43 were rendered negative to Wood's light, as were 20 of 21 infected with *M. canis*. They report no primary irritation or sensitization with concentrations of 2 per cent and 5 per cent but do report that 10 per cent is a primary irritant. In our experience herewith reported, with 2 per cent ointment and 2 per cent tincture, we encountered no evidence of either primary irritation or sensitivity.

LABORATORY STUDIES

Direct-Action Tests in Vitro

Widely used routine mycologic methods of determining fungistatic and fungicidal action of the drug on spores and mycelium have already been carried out by Grunberg and his co-workers.[3] The laboratory evaluation herewith described was decided on as a simple method of studying the direct action of the medication.

Nine out of the large group of children diagnosed as having positive cases of microsporosis capitis ("ringworm of the scalp") were taken at random. A number of hairs, which were fluorescent under Wood's light, were plucked with sterile forceps from the scalp of each child and placed in separate sterile dry containers. After removal and before use in the experiments, all hairs were again examined under Wood's light to ascertain that each was fluorescent.

Several hairs from each source were then placed, in sterile distilled water, sterile petroleum jelly, nonmedicated carbowax ointment, 2 per cent Asterol Dihydrochloride ointment and 2 per cent Asterol Dihydrochloride tincture; one hair was planted in a tube of standard Sabouraud's dextrose medium as a control. In two experiments, petroleum jelly and carbowax ointment were omitted.

After twenty-four and forty-eight hours (and in some instances after eight and twelve hours) and after seven and fourteen days, 1 hair was removed from each container, dipped 6 times in sterile distilled water and planted on Sabouraud's dextrose agar. From most of the hairs that had been immersed in water, petroleum jelly and carbowax ointment, positive cultures were obtained. From none of the hairs infected with *M. audouini*, which had been exposed to 2 per cent Asterol tincture, could this organism be cultured.

One of the patients, L. T., infected with *M. canis*, whose hairs had been exposed to 2 per cent Asterol tincture, gave negative cultural findings after eight hours, seven days and fourteen days, but the cultures were positive after twenty-four and forty-eight hours. From none of the hairs of the 2 other patients infected with M. canis, which had been exposed to 2 per cent Asterol tincture, could the offending organism be cultured. In one case (J. C.) there was no growth at any time after immersion in 2 per cent Asterol ointment; in the 8 other cases there was growth after varying intervals. In the case of L. T., every hair immersed in ointment gave positive cultures, even after two weeks. In three cases, hairs immersed in Asterol ointment for two weeks were still positive; in 4 cases hairs gave positive cultures after one week; in 6 cases there was growth after forty-eight hours, in 5 cases, after twenty-four hours and in 2 cases, after eight hours. (The other 7 were not observed at the eight-hour lapse.)

Figure 1 is a photograph of the culture tubes implanted with hairs extracted from Patient W. J. (*M. audouini* infection) and Patient L. T. (*M. canis*

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¶This drug was provided by Hoffmann-LaRoche, Incorporated, through the courtesy of Dr. Leo A Pirk.

infection). Immersion of the *M. audouini*-infected hairs in 2 per cent Asterol tincture for eight hours or longer inhibited growth; the immersion in two per cent Asterol ointment did not, except after fourteen days. Immersion of the *M. canis*-infected hairs in 2 per cent Asterol ointment did not inhibit growth. Immersion in the 2 per cent Asterol tincture inhibited growth after twenty-four hours and after forty-eight hours but did not inhibit growth in 1 hair after one week and in 1 hair after two weeks. The culture from *M. canis*-infected hairs after immersion in tincture for seven days was contaminated, but this is not clearly visible in the photograph. However, as stated above and as is evident from the table, hairs from the 2 other patients infected with *M. canis* (the zoophilic type) responded more favorably to immersion in the Asterol tincture by showing no growth after twelve hours, the time when the first transfer of hairs was made to the culture medium.

TABLE 1. *Cultural Findings on Hairs Infected with* M. audouini *and* M. canis.

PATIENT	ORGANISM	WATER	PETROLATUM JELLY				
			8 hr.*	24 hr.	48 hr.	7 days	14 days
	M. canis	+ or C†	+	+	+	+	+
W. J.	*M. audouini*	+ or C	+	+	+	+	+
J. B.	*M. audouini*	+ or C		+	+	+	+
J. C.	*M. audouini*	+ or C		+	+	+	–
L. B.	*M. audouini*	+ or C		C	–	–	–
W. B.	*M. audouini*	+ or C		+	+	–	+
D. E.	*M. audouini*	+ or C		+	+	–	–
F. A.	*M. canis*	+ or C					
P. B.	*M. canis*	+ or C					

*Hours and days indicate time of immersion before removal for culture.
†Contaminated.

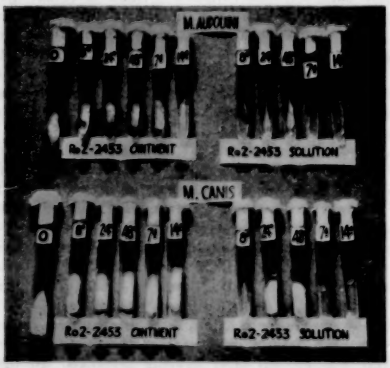

FIGURE 1. *Culture Tubes Containing Dextrose Medium Inoculated with Infected Hairs from Patients W. J.* (M. audouini) *and L. T.* (M. canis).
The hairs were immersed in Asterol (Ro2-2453) ointment and Asterol (Ro2-2453) tincture for the length of time marked on each tube. The large tube marked "O" is the control; + indicates growth; –, no growth.

CLINICAL STUDIES

Sixty-one children affected with microsporosis capitis, "ringworm of the scalp," were treated with Asterol Dihydrochoride — 2 per cent ointment in carbowax base or 2 per cent tincture or both. The diagnosis in each case was confirmed by mycologic examination: direct microscopical examination and culture. Sixteen were infected with the animal type, *Microsporum canis*, and 45 with the human type, *Microsporum audouini*. Those responsible for their care, — the patients' mothers in most cases, — were carefully instructed in all the details of treatment, which comprised medication, shaving of the head when indicated, proper shampooing, sterilizing of combs and brushes if used at all and the sterilization and disposition of the cotton caps worn by the patients.

Thirty-one patients (21 infected with *M. audouini* and 10 infected with *M. canis*) were treated less than three months. Many of these were lost to observation after intervals varying up to ten or eleven weeks. Of these, *none* were clinically or mycologically cured before they were lost. Of the rest, none were cured by the time the observations on which this study is based were completed. There was no agreement among us concerning classification of such a result, other than that the observation was inadequate as a basis for determining the therapeutic effectiveness of the regimen.

Thirty patients were treated for more than three months. Six were infected with *M. canis*; they were from four to twelve years of age. Five of these were cured, clinically and mycologically. In 1, the infection was clinically improved and mycologically still present.

Twenty-four children of those treated for more than three months, — from two to twelve years old, — were infected with *M. audouini*. Five of these were cured, clinically and mycologically. Of these, one was twelve years old, 3 were five years

old and 1 was four years old. In 1 case fluorescence disappeared but cultures were inadvertently not taken; hence the "cure" is not confirmed. Table 2 summarizes these results.

No untoward reactions to the medication were seen in any case. One twelve-year-old girl with dark hair developed a red discoloration of her hair after several weeks' use of the ointment. This persisted for several months during the period of treatment; the cause is unknown.

TABLE 1 (*Concluded*).

PATIENT	CARBOWAX					RO2-2453 TINCTURE					RO2-2453 OINTMENT				
	8 hr.*	24 hr.	48 hr.	7 days	14 days	8 hr.*	12 hr.	24 hr.	48 hr.	7 days	14 days	8 hr.*	12 hr.	24 hr.	48 hr.	7 days	14 days
L. T.	+	+	+	+	+	−		+	+	C	−	+		+	+	+	+
W. J.	+	+	+	+	+	−		−	−	−	−	+		+	+	+	+
J. B.		+	+	+	+			−	−	−	−			+	−	+	+
J. C.		−	+	+	−			−	−	−	−			−	−	−	−
L. B.		C	+	C	+			C	−	−	−			+	−	C	−
W. B.		+	−	+	+			−	−	−	−			+	+	+	+
D. E.		−	−	−	+			−	−	C	−			−	+	−	−
F. A.							−		−	−	−		+		+	−	−
P. B.							−		−	−	−		−		+	−	−

sisted for several months during the period of treatment; the cause is unknown.

DISCUSSION

A new antifungoid preparation, Asterol Dihydrochloride, used in 2 per cent strength in a carbowax ointment base and in a 2 per cent tincture, has been studied mycologically and clinically in 61 cases of microsporosis ("ringworm") of the scalp. Scalp hairs infected with the animal type (*Microsporum canis*) and the human type (*Microsporum audouini*) were immersed in these preparations for varying lengths of time. The tincture inhibited growth in all the hairs infected with *M. audouini*, but in 1 hair infected with *M. canis* there was no inhibition after twenty-four and forty-eight hours.

These in-vitro experiments were suggested to us by the work of Robinson,[5] who reported that infected hairs immersed in various liquids and ointments for a number of days still grew positive cultures. Reiss[6] reported that spraying *M. audouini*-infected hairs with 2 per cent Asterol tincture rendered them culturally negative. He did not wash the hairs before planting them; he was primarily interested in studying the prophylactic effectiveness of spraying motion-picture theatre seats with the tincture as a means of controlling the spread of infection in children.

Our in-vitro experiments with the ointment showed complete inhibition of growth in only one case of *M. audouini* infection. There was some growth at varying intervals in 8 other cases. Whether simple immersion of the infected hair in the ointment adequately reproduces the physical interfacial contacts such as are obtained by rubbing the ointment onto the scalp is a matter of conjecture. In two cases of *M. audouini* infection and one of *M. canis* infection, hairs still produced positive cultures after immersion in the water-soluble carbowax ointment containing 2 per cent of the drug. Kligman and Anderson[7] demonstrated the phenomenon, well known to dermatologists, of the high "rate of cure with a non-fungistatic ointment base." This particular carbowax ointment base did not inhibit the growth of infected hairs by simple immersion.

CONCLUSIONS

Asterol Dihydrochloride, a new antifungoid preparation, in 2 per cent water-soluble ointment and 2 per cent tincture, was used in a laboratory and clinical evaluation. The tincture is more effective than the ointment, as measured by in-vitro tests on infected hairs; neither was 100 per cent effective in suppressing viability, although the tincture did inhibit growth in all the hairs infected with *Microsporum audouini*.

TABLE 2. *Results in Cases of Microsporosis Capitis Treated with Asterol Dihydrochloride Ointment and Solution.*

	NO. OF PATIENTS	NO. OF PATIENTS CURED
Patients treated less than 3 months:		
Infected with *Microsporum canis*	10	0
Infected with *Microsporum audouini*	21	0
Totals	31	0
Patients treated longer than 3 months:		
Infected with *Microsporum canis*	6	5
Infected with *Microsporum audouini*	24	5
Totals	30	10

Sixty-one children were treated, 31 for less than three months. Of these none were "cured," but because of the short period of observation definite conclusions are not drawn from these cases. Thirty children were treated for more than three months; 5 out of 6 cases of *M. canis* (animal type) infection were cured and 5 out of 24 cases of *M. audouini* (human type) infection were cured.

No distinction was made in the clinical cases between the effect of treatment with ointment alone and that of treatment with tincture alone.

The ideal topical preparation for the treatment of microsporosis ("ringworm") of the scalp should have such a consistently high percentage of prompt effectiveness as to endow it with unquestionable specificity. Less than this is no more than progress and should be so designated. The translation of laboratory experiments into evaluation of therapeutic efficiency should be presented with the utmost discretion. More work with a higher concentration should be reported. This drug merits further consideration.

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CLINICAL NOTE

CHILLS AND FEVER FOLLOWING ORAL USE OF PROCAINE AMIDE (PRONESTYL)*

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PROCAINE amide hydrochloride (p-amino-N-(2-diethylaminoethyl) benzamide hydrochloride[1]) has recently been introduced as an effective therapeutic means of controlling ventricular arrhythmias and premature contractions because of its ability to depress the irritability of the ventricular muscle.[2] Unlike procaine hydrochloride, procaine amide is only partially, if at all, hydrolyzed by plasma esterase to p-aminobenzoic acid and diethylaminoethanol; hence its effect is more prolonged.[1, 2] It is now being used also in arrhythmias and premature contractions of auricular origin.[3-5] Thus far, the main toxic effect noted on intravenous administration of the drug is hypotension; toxic effects following its oral use have been described as nausea, vomiting, mental confusion and diaphoresis.[1-4, 6] In the following case report the oral administration of the drug was followed by high fever and shaking chills.

Case Report

L. M., a 48-year-old businessman, complained of short episodes of rapid beating of the heart over a period of 15 years. The palpitations were described as abrupt in onset and in cessation. During these periods he also had headache, dizziness and shortness of breath but no chest pain. On one such occasion he had fainted. The episodes occurred both at rest and on effort. The paroxysms seemed to be more frequent when the weather changed. He had learned from past experience to stop the episodes by extending his neck at an acute angle.

There was no history of heart disease or thyroid dysfunction. The patient drank liquor in moderation. He had smoked an average of 7 cigars daily for the past 18 years. Quinidine had been prescribed in the past, but he had not taken it regularly; he believed that it had no effect on the palpitations.

Physical examination was negative. The blood pressure was 116/70 and the pulse rate 60, with regular sinus rhythm. The heart was normal in size. Heart sounds were normal. No murmurs were heard. No episode of tachycardia was observed.

Urinalysis was negative. A complete blood count was normal. The erythrocyte sedimentation rate was 7 mm. in 1 hour (Westergren method). The blood sugar was 92 mg. per 100 cc. The basal metabolic rate was −18 per cent. An electrocardiogram was within normal limits.

The diagnosis was paroxysms of supraventricular tachycardia, cause undetermined, with no heart disease.

Procaine amide hydrochloride (Pronestyl) was prescribed, 2 capsules (each 0.25 gm.) four times daily. The patient was advised not to change his routine otherwise and was permitted to continue smoking.

Within a week the patient reported that he was experiencing weakness and sweating during the day and that when he reached home each evening he suffered shaking chills and felt feverish. He also noted that he felt no palpitations while taking the drug. When he had stopped taking the Pronestyl to ascertain whether his chills and fever were related to its administration, he suffered no further from these symptoms. He was advised to begin taking the Pronestyl again. Within 24 hours he again experienced a shaking chill while at dinner. When he was examined on that same evening he was having a chill and his rectal temperature was 104°F. There was no hypotension. Physical examination was otherwise negative except for a commensurate tachycardia of 108 with regular sinus rhythm. Symptomatic treatment was given and the patient was kept in bed. Pronestyl medication was stopped. Within 24 hours his temperature was normal and he was asymptomatic. Further attempts to persuade the patient to take Pronestyl in order to reproduce the described effects, if possible, have been unsuccessful.

Comment

In the absence of any other adequate explanation for this patient's febrile reaction with shaking chills, it is logical to assume that the procaine amide was the excitant. This patient gave no history of sensitivity to procaine, which he had received on several past occasions when undergoing dental surgery.

As experience with procaine amide increases, it is likely that similar reactions will be encountered. At present it is well to record this type of febrile reaction, presumably due to procaine amide, for the benefit of physicians who are prescribing the drug.

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MEDICAL PROGRESS

ACTH AND CORTISONE IN THE TREATMENT OF OCULAR DISEASE (Concluded)

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CLINICAL ASPECTS OF PARENTERAL ADMINISTRATION OF ACTH AND CORTISONE

As one might expect, the type of ocular lesion has not determined which of the two hormonal agents should be employed. Olson and others,[12] in summarizing their experiences with ACTH and cortisone, obtained generally identical results with both drugs in a series of 51 cases. These investigators reported similar findings at the Second Clinical ACTH conference,[10] at which 97 cases were added to the original series. In some cases, there may be physical findings that justify the selective use of one of the hormones. Thus, in patients with such clinical states as essential hypertension, hypertension secondary to renal disease or cardiac decompensation, the pharmacologic effects of cortisone may temporarily be better tolerated. Ultimately, the same limitations will probably arise. In a certain few cases resistance or allergy to the pituitary hormone may be encountered, but these aspects of therapy are not peculiar to ocular disease and will not be further discussed.

As in any type of clinical problem, the successful therapeutic use of these agents in ocular disease will require the physician to be acquainted with the indications for their administration, the various physiologic indices employed to evaluate adequacy of dosage, the pharmacologic side-effects and other features of administration that may limit their usefulness. In this regard, much has been written.[27-34, 35] The value of proper base-line studies, however, cannot be denied, and admission for institutional care is certainly desirable — at least in the early stages of treatment. The apparently limited nature of many ocular lesions in no way justifies the attitude that patients with eye disease require less critical selection and care than patients with more generalized afflictions. The same limitations of hormonal treatment will be encountered, and the incidence of undesirable effects will in the long run be essentially similar. It is advisable that each patient be thoroughly evaluated before long-term parenteral therapy is given for relatively minor eye lesions. Certain of the latter may be controlled effectively by topically administered cortisone or other forms of therapy. It is conceivable that physicians, in treating acute ocular inflammatory diseases, will be reluctant to involve many patients in expensive hospitalization and laboratory studies, knowing that the lesion is of the type that responds to a few doses of the hormone. If this therapeutic approach is followed and is found inadequate for one reason or another, it is essential that patients undergoing extended treatment be examined frequently, with attention being directed to the over-all clinical condition and to a minimum of laboratory data.

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DOSAGE

In general, the initial dosage of ACTH for an adult with ocular inflammatory disease should approximate the equivalent of 100 to 150 mg. a day of the Armour standard LA-1-A. If satisfactory results are seen within the first two or three days, the daily dosage can be reduced to approximately 75 mg. If good results are not noted by the third or fourth day, it is probable that the over-all response to ACTH will be limited. Under these circumstances, continuation of the drug at a daily level of 60 mg. to 80 mg. is adequate, provided the several physiologic indices reveal that adrenal hyperfunction is being maintained. Gordon[36] has shown that the effects of a given intramuscular dosage of ACTH can be greatly enhanced by the slow intravenous infusion, but this somewhat less practical measure does not supplant the present program of interrupted doses at four- to eight-hour intervals. It is possible, however, that a single intravenous administration of 20 mg. of ACTH over six to eight hours may prove sufficient to control many early acute inflammatory lesions of the eye.

For comparable cases treated with cortisone, the initial dosage schedule should allow for approximately 200 mg. to 300 mg. a day for the first two to five days. Thereafter, according to the type of lesion being treated, the dosage may be adjusted to a lower level. In the acute nonspecific inflammatory group five days of treatment often suffice, but 100 mg. to 150 mg. daily for two or three more days will be necessary for complete resolution in some cases. Unlike the program with ACTH, a gradual withdrawal from intramuscular cortisone therapy is not necessary, in view of its slow absorption from the muscle depots.

In the chronic inflammatory lesions, continuation of therapy at a daily level of 100 mg. to 150 mg. seems adequate once initial improvement has been achieved. At this dosage there may be evidence in the physiologic indices, such as eosinopenia and

leukocytosis, that adequate levels of the hormone are being maintained. Further clinical gains, however, may be seen when certain of the indices have returned to normal.

The question now arises concerning what form of therapy can give the best long-term results in patients with chronic inflammatory lesions. Several possible therapeutic regimens will be considered. The most promising of these is to attain an initial maximum improvement with parenterally given cortisone or ACTH and to continue therapy with local administration of cortisone over a period of weeks or even months. In this way the early benefits may be maintained and in some cases additional improvement may be witnessed. Certainly by the third week of parenteral therapy further regression of the lesion is usually slow and, in view of the possible pharmacologic effects, continuation of the intensive therapy does not appear justified. Exceptions to this therapeutic program will be encountered, and individualization of case therapy may often be necessary for optimum results. In patients on long-term regimens of parenterally given cortisone, adrenocortical involution has been observed by Sprague and others[37]—a condition that may jeopardize the continuation of remissions after cessation of therapy. Patients on such a program may benefit from the interval stimulation of cortical function by three to five days of ACTH, both during and immediately after the use of cortisone. Here the intravenous use of ACTH can accomplish this effectively in a short period of time.

Another possible program is one of interrupted parenteral therapy after an initial course of intensive treatment. We have found this use of ACTH somewhat disappointing. Interrupted doses of ACTH have frequently produced resistance or allergy to the hormone. It is questionable, furthermore, whether any but transient influence is exerted on a chronic lesion by the periodic intramuscular injections of ACTH when given in the usual aqueous solutions. Attempted maintenance of the initial improvement with parenterally given cortisone in small doses is somewhat cumbersome and expensive and would be justified only when one could not obtain adequate control with the topical use of the hormone. The results of repeated courses of intensive parenteral therapy have not been reported, but this may have limited value in the chronic inflammatory eye lesions.

The value of the long-acting ACTH preparation in the treatment of ocular disease has not been demonstrated adequately to date. The experiences of Wolfson and others[38] and Howard and others[39] in the general use of long-acting ACTH suggest that at least once-daily (and preferably twice-daily) injections are indicated. In our hands their value has been limited to maintenance therapy in the group of patients with acute inflammatory lesions and selected patients with recurrent inflammatory diseases. They offered potential promise in the long-term control of chronic inflammatory lesions, but Wolfson and others[38] found the dosage often dangerously high and the therapy impractical. At the time of this writing, the long-acting vehicles have not been released for general use.

General Considerations

Certain general features of the behavior of ACTH and cortisone in the treatment of eye disease possibly warrant particular mention. Noteworthy is one observation that pain arising from a variety of types of ocular lesions is often relieved not only by the parenteral injection of either hormone but also by small amounts of locally applied cortisone. This is true in such conditions as keratitis, corneal burns and ulcerations. This relief of corneal pain seemed to be a specific effect of the corticosteroid on sensory endings, as suggested by the observation that it occurred in some cases in which visible alteration in the lesion itself had been lacking. Clinically, however, we have been unable to demonstrate any alteration in corneal threshold to light touch, and Grokoest and others[40] recently reported the lack of analgesic effect of ACTH and cortisone in patients with rheumatoid arthritis. Relief of pain is probably dependent on the antiphlogistic properties of the 11-oxycorticosteroids.

Of equal interest are the observations that have been made on the effects of ACTH and cortisone on ocular vascularization and hyperemia. In an early study Jones and Meyer[41] observed inhibition by locally applied cortisone of chemically-induced vascularization of the rabbit cornea; they suggested several possible mechanisms of action. In clinical experience, vascularization occurring in several types of corneal lesions has been inhibited by ACTH and cortisone. To a similar extent, the hyperemia associated with many ocular lesions is controlled, reflecting the well known property of cortisone and ACTH of suppressing inflammations of diverse origins.[42-44] The nonspecificity of this phenomenon is now accepted. In the eye, this has been demonstrated by Steffensen and others[17] during the treatment of patients with dendritic keratitis when the inflammatory reaction and pain were controlled rapidly but the corneal lesion remained active during the period of topical cortisone therapy. Similarly, Olson and others[18] reported the hyperemia accompanying an early transitional-cell carcinoma of the limbus to have been effectively suppressed during a brief period of parenteral cortisone therapy. Since inflammation is inhibited nonspecifically, the favorable clinical results of ACTH and cortisone treatment in ocular diseases with hyperemia in no way help to establish the respective etiologies. Unfortunate delays in diagnosis may result, as in the case just mentioned, unless appropriate study is first carried out.

There is no question that locally administered cortisone can resolve many acute nonspecific lesions of the anterior eye. That it accomplishes this effectively is suggested by the seemingly small amounts of cortisone that have been found necessary. The widely employed therapeutic program of 1 to 2 drops of a 1:4 suspension every hour would deliver to the entire conjunctival sac approximately 0.2 mg. per drop or about 2.5 mg. per treatment day. Considering the total body basal requirements for homeostasis to be approximately 25 mg. per day,[37] the amounts so used in the eye thus become exceedingly great. Loss of the suspension, however, through spillage from the conjunctival sac and drainage through the lacrimal passage probably accounts for the major portion. The minimal requirements of cortisone for control of ocular inflammation by this route have not been determined, and this therapeutic program may be excessive. It seems likely, should quantitation be found possible, that the requirements will be nearer physiologic than pharmacologic levels.

We have mentioned above that topically given cortisone has limited value in the treatment of many posterior-uveal-tract lesions. This is not surprising when we consider the improbability of conjunctivally applied cortisone's ever reaching the vitreous or afferent vessels of the retina in therapeutic amounts. In addition, we have observed an occasional case of delayed and incomplete control of severe anterior-segment inflammation, such as acute iritis, when cortisone was used as a collyrium only. This we attributed to an inadequate amount of the corticosteroid reaching the anterior chamber, possibly through a limitation in the rate of diffusion across the corneal membrane. This appears to have been a reasonable explanation, particularly in view of the recent observations of Dougherty.[44] This investigator has demonstrated that there is a direct relation between the size of an experimentally-induced histamine inflammatory lesion and the amount of cortisone necessary to achieve its inhibition. Thus, certain severe inflammatory lesions of the anterior eye may not be controlled with topical cortisone because the corticosteroid requirements have exceeded the rate of its diffusion across the cornea.

Physiologic Basis for the Use of ACTH and Cortisone in Ophthalmology

In reviewing the early experimental uses of cortisone and ACTH in ophthalmology, the observation can be made that three separate groups of clinical investigators in the field were motivated in their studies by somewhat different considerations. That these workers had much in common will subsequently be shown. In this discussion, as in any that pertains to mesenchymal disease, it becomes obvious that one cannot divorce the several concepts of pathogenesis from those that underlie the endocrine therapy of seemingly nonspecific inflammatory processes. The corticosteroids and ACTH are essential to the homeostasis of a wide variety of physiologic systems. Thus, the sensitive and seemingly specific response of certain inflammatory ocular lesions suggests that treatment with these hormones is, in a broad sense, a form of local replacement therapy. Lansbury,[45] in writing similarly of the rheumatic state, considered it comparable in some respects to the endocrine therapy of diabetes mellitus wherein exogenous insulin, in the situation of relative islet-cell insufficiency, restores to normal the homeostasis of carbohydrate metabolism.

Gordon and McLean[3] indicated that they considered certain lesions of the eye to be analogous in some respects to the morphologic alterations of rheumatoid arthritis. Both ocular and joint structures are basically constituted of mesenchymal tissues, and concurrent nonspecific inflammation is not rare. In view of the successful use of ACTH in other diseases involving the mesenchyme, it was logical to investigate the value of the hormone in patients with ocular diseases. As we have reviewed above, many inflammatory eye lesions have been controlled effectively by ACTH or cortisone. This cannot be used as direct evidence, however, that the respective lesions reflect a primary disturbance in collagen and connective-tissue structures. Subsequent studies may demonstrate that the pathogenesis of certain ocular lesions is similar, if not identical, to that occurring in the acute rheumatoid joint. In this conceivable circumstance, generalized mesenchymal disease might arise independently of the level of adrenal function yet within its physiologic limits. The only primary role for the adrenal glands would thus be therapeutic, and only so at pharmacologic levels of cortical activity.

In our initial studies with Olson and others,[4] we were concerned more with the physiologic mechanisms involved in traditional therapy than with concepts of pathogenesis. We postulated that the artificially-induced fever employed in treating certain ocular inflammatory diseases achieved its beneficial results by causing adrenocortical hyperfunction. This concept could derive some physiologic support from the previous experimental work of Sayers and Sayers[46]; these investigators demonstrated that fever and killed bacteria were means of accelerating adrenocortical function in animals. It was accepted generally that stress of many such origins evoked in the intact organism, as one of several hormonal responses, an increased elaboration of the 11-oxycorticosteroids that have been shown to increase the capacity for survival. A subsequent clinical study by Arendshorst and Falls[47] demonstrated that intravenously injected killed typhoid organisms did in effect produce a temporary state of adrenal hypercorticism in patients with inflammatory ocular disease. That the induced

adrenal hyperfunction was the basis for the clinical improvement was suggested by the observation that therapeutic benefits seemed to parallel the degree of adrenal response.

During the early period of our studies with ACTH and cortisone, we were impressed by the clinical histories of certain patients that suggested that functional changes in the neurohypophyseal-adrenal system itself might be important in the pathogenesis of many nonspecific ocular inflammatory lesions. It was noted in these patients that the inception of the inflammatory lesions frequently occurred during or shortly after periods of great stress, particularly those associated with psychic tension. These observations have subsequently been reaffirmed in an additional number of patients. This is by no means a new concept, for Harrington[48] has drawn attention to a similar possible relation of stress to certain types of ocular inflammatory diseases. It was reasonable to postulate, in accord with the general-adaptation theory of Selye,[49] that particular stress states might lead directly to ocular changes that would be dependent to a great extent on the altered neurohypophyseal-adrenal function and yet be quite independent of hypersensitivity. The eye, by virtue of its extensive vascular bed, delicate connective-tissue framework and prominent fluid media, may be more sensitive than many other organs to alterations in the level or pattern of neurohumoral activity. Since the ocular system has such a high index of total activity and since so much of its structure is readily accessible to direct visualization, one may speculate that many of the "stress" lesions would occur and be recognized early in this area.

As for evidence of direct hormonal action on the mesenchyme, Baker and Castor[50, 51] have demonstrated in the rat that percutaneous and whole cortical extract can produce structural alterations in normal connective tissue with a reduction in the number of fibroblasts. Schneebeli[52] has reported fibroblastic alterations and changes in the ground substance of adrenalectomized cortisone-injected mice. More recently, however, he and his associates[53] have questioned the validity of these changes as reflecting pure steroidal influence. In a recent publication Cornman[54] reported that striking injury to fibroblasts could be demonstrated when desoxycorticosterone was incubated with tissue cultures of heart fragments. Finally, Selye[55-57] states that desoxycorticosterone, usually in the presence of excess sodium chloride, can produce lesions in the rat that are pathologically similar, in some respects, to vascular lesions seen in certain mesenchymal diseases of man. Although these laboratory observations do not provide much support for the concept of "stress" lesions of the eye, they do represent the framework within which ophthalmologists may study further the etiologies of many inflammatory diseases of the eye heretofore considered nonspecific. In this respect, recent observations by the authors have proved provocative. On three occasions at this hospital a nonspecific episcleritis was observed in a patient with well established Addison's disease in whom the previous implantation of an excessive number of desoxycorticosterone pellets had led to moderate hypertension. It should be recorded that prior to the onset of two of the typical lesions the sympathomimetic amphetamine sulfate had been given in the course of experimental therapy, but its significance in the development of the lesions can be questioned. The topical use of cortisone on the last two occasions resolved the inflammation within twenty-four hours, whereas ten days of therapy with antibiotics and analgesic ointment had failed to control the initial lesion. We believe that this single clinical observation warrants mention in view of the rarity of this type of acute nonspecific inflammatory lesion in patients with established adrenal insufficiency and in view of the apparent etiologic significance of desoxycorticosterone.

It is reasonable to ask why benefit often follows the use of ACTH in certain patients with nonspecific inflammatory lesions if it is maintained that these lesions result from the accelerated adrenocortical function associated with stress, as cited above. To answer this is only to extend the original postulate. One must consider the probability, however, that the total response of the organism to stress is far different from the relatively singular effects of ACTH or cortisone when these hormones are given therapeutically. Dissimilarities in the quantitative and perhaps in the qualitative aspects of cortical response, as well as the provocation of the many neurohumoral mechanisms during "physiologic" stress would lead, conceivably, to ultimate differences in tissue morphology from those produced by ACTH alone. A basic role for the sympathetic system itself and for certain adrenal medullary pressor substances, as well as for the corticosteroids, is a reasonable contention, but to define their relative importance in the elaboration of "stress" lesions will require considerable study.

Woods,[8] in his studies of ocular inflammation, considered the use of ACTH and cortisone on the grounds that hypersensitivity phenomena involving other systems had been shown to respond dramatically to these agents. His theories in regard to the etiology of certain ocular inflammatory diseases[58] have been recognized widely for many years, and the use of these new agents in this respect was a logical development. The temporary hormonal inhibition of the morphologic expressions of hypersensitivity[59, 60] cannot suggest any specificity of the accompanying inflammation. It is now well known that ACTH and cortisone suppress inflammation of diverse etiologies,[41-43] and this has restricted the utilization of the hypersensitivity concept in ocular inflammatory disease. Data are ac-

cumulating to show that although tissue manifestations of hypersensitivity may be inhibited there is usually no reduction in the titer of circulating antibodies except during prolonged administration of the hormones.[61] Tissue antibodies may be altered, and one would hesitate to state categorically that there is no change in the nature or amount of the specific antigen. Conceivably, the parenteral administration of ACTH and cortisone might have some pharmacologic effect on the particular injured tissue, whether ocular or otherwise, from which antigenic protein is presumably being released. This seems unlikely, and it is reasonable to contend that sustained remissions should not occur in patients with ocular inflammatory disease if hypersensitivity is accepted as the cause of the lesion. The often continued remission that has been observed to follow the local use of cortisone in iritis, for example, certainly does not suggest that hypersensitivity is fundamental to that particular lesion. Here one might expect a relapse to have occurred as soon as the inhibitory effect of cortisone was removed

It is apparent so far that the adrenal cortex has been involved, directly or indirectly, in the pathogenesis of nonspecific ocular inflammatory disease. It is apparent also that certain aspects of pathogenesis cannot be considered unique in their application to ocular diseases. It is beyond our purpose, however, to consider the more widespread mesenchymal lesions in the light of this discussion, for much has already been written in this regard.[62, 63] Since the early clinical investigators approached the experimental trial of ACTH and cortisone in ocular inflammatory disease along three essentially different lines of reasoning, we have been considering pathogenesis accordingly. It was an arbitrary division for the purposes of review, and should not be interpreted as meaning that these investigators necessarily fostered or held rigidly to the concepts with which their names have been associated here. That differences in these several concepts are more apparent than real is borne out, for instance, by acknowledging that hypersensitivity does affect the mesenchyme with morphologic alterations in the collagen, ground substance and other connective-tissue structures.[62] In addition, it is possible that disruption of homeostasis in the complex neurohumoral systems governing adrenal function, such as would occur in the "stress" state, may predispose the patient to the development of hypersensitivity. In a similar sense, Dougherty and Dougherty[64] have postulated that desoxycorticosterone may unmask latent hypersensitivity through its property of modifying the action of the 11-oxycorticosteroids that inhibit the phenomenon.

Recent experimental studies by several groups have brought new attention to a unique relation between several humoral factors whose present roles, both physiologic and pathologic, have not been clearly delineated. Employing the protamine titer[65] as an indirect and approximate quantitative index, Smith and others[25] have frequently observed a rise in the blood level of heparin or a heparin-like factor during the administration of ACTH and cortisone. These observations were made initially in patients undergoing hormonal treatment for a variety of ocular diseases. Early in the latter study we considered the possibility that the hormonally-induced release of heparin or a heparin-like substance might be necessary for, or at least contribute to, the therapeutic benefits that are seen with ACTH and cortisone. It was anticipated that parenterally given heparin might support this thesis if it could be shown that favorable changes in acute nonspecific inflammatory lesions followed its administration. Four such experiments by Steffensen and Ivy[66] have demonstrated that intravenously injected heparin can favorably modify certain features of acute plastic iritis but to a lesser extent than has been observed with ACTH or cortisone. Bick and Wood[67] recently reported that heparin in the experimental animal not only effected a partial resolution of a hypersensitivity-induced ocular inflammatory lesion but actually inhibited the development of inflammation when given prior to the attempted induction.

It is of further interest in this respect that the reports of Glick,[68] Adams and others[69, 70] and Dorfman and Moses[71] have cited evidence that the increased levels of a hyaluronidase inhibitor found in the blood of patients with acute rheumatic fever could be lowered significantly during treatment with ACTH. Hakanson and Luft[72] and Schmith and Faber[73] had reported similar results in 2 patients with rheumatoid arthritis. Logan[74] and her associates, however, observed significantly increased titers of serum antihyaluronidase during the clinical improvement in patients receiving ACTH for diverse rheumatic syndromes. In conjunction with others, Glick[75-77] had previously demonstrated similar increased levels of the inhibitor in a number of pathologic conditions, particularly in acute febrile illnesses and stressful lesions associated with tissue destruction. With Good and others[75] he postulated a significant role for the adrenal glands in this regard and presented preliminary data to indicate that the release of the hyaluronidase inhibitor into the blood of animals under stress did not take place after adrenalectomy. Glick[68] reported that ACTH, when given to children with hypoglycemia, produced a significant rise in the hyaluronidase inhibitor of serum. Recently he and Sylvén[79] have presented indirect evidence that the long-studied antihyaluronidase substance is possibly a heparin-lipoprotein complex that can be obtained from tissues rich in mast cells. That heparin, in addition to its antithrombin effect, possesses the property of inhibiting hyaluronidase

has been known from the earlier reports of Meyer[80] and McClean.[81]

From these observations on changes in the serum-hyaluronidase inhibitor levels and in blood-protamine titers, it appears that the corticosteroids have some regulatory influence on the heparin level or on its activity in blood. These findings may assist in correlating the observation that heparin can modify an acute inflammatory lesion[67] with the many reports that ascribe to cortisone a similar property.[42, 43] The importance of heparin to the hyaluronidase-inhibiting effects of certain adrenocortical steroids[82] cannot be defined at present. The fact that both heparin and hyaluronic acid are prevalent mucopolysaccharides of the mesenchyme[83, 84] suggests a possible functional relation of the former to the hyaluronic-acid–hyaluronidase system. Elucidation of this is essential, of course, before we can understand their role in the pathogenesis and treatment of many ocular and systemic inflammatory diseases.

A new and unique approach to the further understanding of many ocular (and, indeed, many other) lesions has been presented recently in the reports of Rebuck and others.[85, 86] These investigators have utilized a technic that makes possible the in-vivo study in man of the chronologic alterations of exudative cells evoked in an experimentally-induced area of inflammation. By routine staining and by histochemical study of more specific intracellular enzyme systems they have attempted to correlate not only the pattern of cytologic behavior in the skin "windows" with the type of presenting ocular disease but also the reaction induced in both by the administration of ACTH and cortisone. Their reports suggest that certain ocular lesions are reflections not necessarily of specific disease localized in the orbital structures but of abnormalities in cellular response of a more widespread nature. These may be dependent on an altered hormonal state in some cases and in others on a basic deviation of cytologic behavior evoked nonspecifically by a variety of noxious stimuli.

Summary

ACTH and cortisone have already assumed a ranking place in ocular therapeusis. The greatest benefits have been found in their use in early, nonspecific inflammatory lesions of the eye. Their availability should not be presumed to lessen the need for both their appropriate use and the proper diagnosis of ocular disease. They are agents of manifold properties; like a two-edged sword, they are capable of curing a diseased eye at the expense of the patient's well-being.

Consideration has been given to currently accepted therapeutic programs and attention has been called to certain limitations that may be encountered. We have reviewed, in addition, several of the current theories of pathogenesis of acute nonspecific inflammatory diseases of the eye and have presented the physiologic basis for the use of ACTH and cortisone in the treatment of such lesions.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 37521

PRESENTATION OF CASE

First admission. An eighty-year-old woman was admitted to the hospital because of diarrhea.

Six months prior to admission the patient noted the onset of foul-smelling diarrhea, with 4 to 5 loose stools a day; she noted that they caused an oily film on the water. This was in marked contrast to her previous state of mild chronic constipation. She also noted "gas" and had occasional episodes of nausea and vomiting. There were no definite abdominal cramps, but there was some vague abdominal discomfort. Shortly after the onset of symptoms a gastrointestinal series showed a normal esophagus and some gastric and duodenal dilatation with diminished peristalsis. The dilatation was most marked in the duodenal loop, where the barium had a tendency to pool; although the loop was demonstrated as far as the ligament of Treitz, no specific obstructing lesion was made out. A barium-enema examination was negative. The patient continued to have diarrhea; one month prior to admission she first noted abdominal distention, accompanied by some general discomfort but no localized tenderness. Three weeks prior to admission she had a few days of moderately severe left-upper-quadrant tenderness that was unrelated to eating. One week before admission bilateral edema of the lower extremities appeared and persisted. For a few years she had intermittent lower-leg edema that subsided with rest; this was usually unilateral and was attributed to varicosities. At this time the serum protein was 6.3 gm. per 100 cc., the blood lipase was normal and a stool examination showed a lowered trypsin content. Her weight had fluctuated during the course of the illness: 170 pounds at onset, 130 pounds one month prior to admission and 140 pounds on admission. There had been no bloody or tarry stools or hematemesis. For the ten days before entry she received pancreatin, menadione, and vitamins and was on a low-fat, low-carbohydrate diet. For a few months she had received liver injections.

She had always had remarkably good health. She had had an appendectomy 40 years previously, right mastectomy for a "lump in the breast" thirty years previously and an operation for hammer toe one year previously.

Examination revealed a thin woman who appeared somewhat weak but in no acute distress. The thyroid gland was approximately twice the normal size; it was a diffuse non-nodular enlargement. An old right-mastectomy scar was visible. The abdomen was markedly distended. There was no tenderness or palpable organs or masses. Rectal examination was negative except for hemorrhoids. There was bilateral pitting edema to the knees and some stasis dermatitis.

The temperature was 99°F., the pulse 88 and the respirations 20. The blood pressure was 120 systolic, 70 diastolic.

Examination of the stools showed them to be soft, bulky and greasy, with a normal number of undigested muscle fibers; analysis showed +++ soaps and split fat and a normal amount of neutral fat. The urine was normal. Examination of the blood revealed a hemoglobin of 10.5 gm. and a white-cell count of 2600, with a normal differential. The nonprotein nitrogen was 30 mg., the fasting blood sugar 95 mg. and the total protein 5.71 gm. per 100 cc., with an albumin-globulin ratio of 2.0. The serum amylase was 31 units per 100 cc., the serum lipase 0.8 cc. and the van den Bergh reaction within normal limits. A cephalin-flocculation test was + in 24 and 48 hours, and the prothrombin time was 24 seconds (normal, 20 seconds). A bromsulfalein test showed 7 per cent retention. The glucose-tolerance curve was within normal limits. A tuberculin test was negative. A vitamin A tolerance test (200,000 units, by mouth, in oleum percomorphum) showed at the start 0.79 units per cc.; at 1 hour, 0.67 units per cc.; at 2 hours, 0.68 units per cc.; at 5 hours, 1.24 units per cc.; and at 6 hours, 1.13 units per cc. The carotenoids averaged .51 units per cc. An x-ray film of the chest showed the lung fields to be large and bright, with prominent linear densities throughout. The diaphragmatic motion was moderately limited. The heart and aorta were unremarkable. A gastrointestinal series was negative except for a small hiatus hernia and deviation of the trachea and esophagus to the right in the region of the suprasternal notch, with compression of the trachea anteriorly in this region. Parencentesis yielded 2300 cc. of cloudy amber fluid with specific gravity of 1.010. The fluid contained 770 red cells per cu. mm.; culture and guinea-pig inoculation were negative. Cytologic examination was negative for tumor cells.

At peritoneoscopy the liver, stomach and intestines appeared normal and the pelvic organs were slightly inflamed; a few 1- to 2-mm. nodules were seen in the parietal peritoneum, stomach and liver. A biopsy of one nodule showed fat and fibrous tissue with mild chronic inflammation. The patient was discharged on the nineteenth hospital day, with her condition unchanged.

Final admission. She was readmitted one month later because of vomiting. While at home she was on a 3000-calorie diet and received liver injections, pancreatin and menadione. She was almost completely bedridden and had occasional periods of mild confusion. Bowel movements were from one to four per day. She required paracenteses three weeks and one day before admission. Three weeks prior to admission she noted external hemorrhoids, and three days prior to admission she became nauseated and vomited about half a cupful of bright-red blood. One day before admission she vomited approximately a bowlful of dark-brown material and noted that her stools were "very dark" in color.

Physical examination revealed a wasted, chronically ill woman in no acute distress. The mass in the neck was unchanged from the previous examination. The lungs showed decreased resonance on the left and a few crepitant rales at the right base. The abdomen was distended; shifting dullness and a fluid wave could be demonstrated. The thoracoepigastric veins were distended, and the flow was from below. The liver was enlarged and tender, with the edge 4 fingerbreadths below the right costal margin. There was right-costovertebral-angle tenderness. Hemorrhoids were again noted. There was ++++ ankle edema and a few distended varicose veins over the thighs.

The temperature was 99.2°F., the pulse 80 and the respirations 20. The blood pressure was 100 systolic, 70 diastolic.

The urine examination was negative. A stool guaiac test was ++. Examination of the blood showed a hemoglobin of 10 gm. and a white-cell count of 7400, with a normal differential. The total protein was 5.71 gm., with an albumin-globulin ratio of 1.7, and the nonprotein nitrogen 27 mg. per 100 cc. The prothrombin time was 26 seconds (normal, 19.5 seconds). The serum calcium was 8.7 mg., the phosphorus 3.0 mg. and the phosphatase 4.4 units per 100 cc. The serum lipase was 0.3 cc. and the amylase 22 units per 100 cc. A gastrointestinal series revealed curling of the esophagus, with rather prominent mucosal folds in the lower portion suggesting varices. The fundus of the stomach was pressed on superiorly and laterally by an enlarged mass in the region of the spleen. The stomach was moderately distended and showed delayed emptying; the duodenal loop could not be adequately visualized. A film taken several hours later showed incomplete emptying of the stomach.

On the ninth hospital day the patient vomited small amounts of dark-brown guaiac-positive material. The abdomen was much more distended and very tympanitic, but not tender. Peristalsis was moderately active. A plain film of the abdomen showed the stomach to be tremendously distended. The patient continued to vomit blood with gastric contents, became semicomatose and died on the fifteenth hospital day.

Differential Diagnosis

Dr. Reed Harwood*: "Stool examinations showed soft, bulky, greasy stools, with a normal number of undigested muscle fibers." I wonder how many of us have actually examined enough stools to know what the normal number of muscle fibers is. Certainly much depends on the type of food the patient was eating, how well cooked it was

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and so forth. If this observation was made by an expert, I should pay some attention to it.

My consultant interpreted the vitamin A tolerance test as indicating a slight impairment of absorption of vitamin A. I was told that 1 to 3 units per cc. is the normal range for carotenoids; hence they are definitely low.

Had the edema increased in the interim? Measurements of edema are rather inaccurate; they depend on how impressed the observer is.

DR. BENJAMIN CASTLEMAN: I believe it had increased.

DR. HARWOOD: May I see the x-ray films?

DR. STANLEY M. WYMAN: I am sure it was very difficult to examine this patient adequately. The films from the first examination show a suggestion of a deformed duodenal cap. It is perhaps dangerous to suggest this in view of the fact that the fluoroscopist made no mention of it and it is not part of the official interpretation, but all the available films do show a deformed duodenal cap. The second portion of the duodenum is greatly dilated; I do not see the cause for this (Fig. 1). The barium-enema examination was not remarkable. There is much arteriosclerosis in the aorta, which is not unusual at her age. The gastrointestinal series made about six weeks after the first series again demonstrates what to my mind is suspicious of a deformed duodenal cap and again shows a much dilated second and proximal third portion of the duodenum. I do not see a lesion to account for this, and I cannot say more than that it is dilated. I would worry about some lesion in the region of the pancreas.

FIGURE 1. *Gastrointestinal Series.*
Arrow indicates the point at which the duodenum is obstructed. An organic lesion cannot be seen on the film.

DR. HARWOOD: Have you an x-ray film showing the stomach being pressed on?

DR. WYMAN: The next films, taken about seven months later, show this pressure on the superior portion of the stomach. There is definite evidence of esophageal varices. There is a large amount of fluid in the abdomen and some gas in loops of bowel — without frank obstruction, however. The stomach seems to be severely obstructed, and a film taken one day later shows tremendous distention of the stomach. This film of the chest shows what appears to be a soft-tissue mass indenting the trachea on its left side — apparently the enlarged thyroid.

DR. HARWOOD: Are you impressed with the lung fields? Do you think they are free of disease?

DR. WYMAN: The lung fields do not seem particularly unusual for a woman of eighty; I think she had a fair degree of emphysema and fibrosis.

DR. HARWOOD: At the outset I want to exclude the tumor of the breast as having anything to do with the present illness. If she had a carcinoma of the breast at that time and, if it were to recur, it would have done so before thirty years had elapsed. Another thing I am not going to pay much attention to is the thyroid gland, which was enlarged and apparently did not change during the several months that she was under observation. I expect it was a colloid goiter. The physician may have been feeling a nodule that pressed on the trachea and displaced it. I am also going to exclude sprue because the ascites would be quite unlikely except in extreme cases of malnutrition; there was no glossitis or a macrocytic anemia, and the patient did not respond to measures that are ordinarily effective in sprue — especially the liver extract.

Bulky, greasy stools point strongly in the direction of some lesion of the pancreas or some deficiency in the external secretion of the pancreas. When the pancreatic ducts are occluded one would expect a rise in the serum amylase and serum lipase; this may indeed have happened at the onset in this case. I assume that the pancreatic ducts were occluded for the six months or more that the disease was going on and that only later in the illness were the studies of the serum amylase and lipase performed; by then perhaps the acinar glands had atrophied somewhat and less of the amylase and lipase were being made. The determinations are not particularly helpful to me. Could this patient have had acute pancreatitis? The absence of an acute onset, with pain and fever, leads me to exclude such a diagnosis. She had a chronically downhill course. Chronic pancreatitis can produce symptoms such as fatty diarrhea. However, the absence of episodes of pain and fever makes this

diagnosis unlikely. Pancreatic lithiasis also can produce fatty stools, but no stone was noted and the characteristic pain was not present. Hemochromatosis will infrequently produce fatty stools. I think we can exclude hemochromatosis because of the absence of glycosuria and pigmentation. The liver became enlarged only late in the illness, and ascites and hemorrhage are rare in hemochromatosis, although they do occasionally occur.

Tuberculosis occasionally affects the pancreas; it too can produce fatty stools. In this case there was a negative tuberculin test and negative guinea-pig inoculation. I am a little bothered by the inflammatory nodules on the peritoneum, but the nodules showed no specific inflammation. I think I can safely exclude tuberculosis.

Then I come to tumors of the pancreas. Occasionally a benign tumor will obstruct the pancreatic duct and produce a picture much like the early stage of this patient's illness. A patient with just such a lesion was recently presented at Grand Rounds in this hospital. Much more common, of course, are the malignant tumors. It is usually said that 85 per cent of the malignant tumors of the pancreas cause pain, which this patient did not have. Sixty per cent or more cause jaundice. Ten per cent are recorded as producing definite interference with the external secretion of the pancreas, with fatty stools and diarrhea. Cancer of the pancreas may metastasize to the liver, lungs and local lymph nodes and may cause pressure on such structures as the portal vein and the vena cava. It should be emphasized that there is a strong tendency to spontaneous thromboses of various veins in pancreatic carcinoma.

The liver, which was also involved in this case, was normal early in the disease. No esophageal varices were noted and the liver-function tests were within normal range. Later on the patient developed ascites, pain in the region of the spleen, enlargement of the liver and spleen, esophageal varices, hematemesis — all of these coming on fairly suddenly suggested to me a rather sudden interference with the portal circulation, possibly extension of the tumor or a metastasis to the lumen of the portal vein. The edema of the legs that occurred during the illness could have been due to phlebothrombosis in the leg or pelvic veins, to the ascites itself or to thrombosis of the inferior vena cava. The lungs do not show the metastases that are frequently present in carcinoma of the pancreas.

The findings in the gastrointestinal series are quite suggestive of a lesion in the region of the pancreas interfering with the passage of barium through the duodenal loop. I am a little disturbed by Dr. Wyman's report of a constant deformity in the tip of the duodenal cap. If the tumor extended that far originally, I would also expect jaundice. I cannot explain why jaundice was not present in this case. I am a little disturbed also by the negative biopsy report of the peritoneoscopy, if there were nodules there. I assume that it might be quite difficult to pick up a 1-mm. nodule and be sure that one had it. It would not surprise me if Dr. Castleman said that there were metastatic nodules of pancreatic carcinoma on the peritoneal wall.

DR. EDWARD B. BENEDICT: I would like to make a comment about the peritoneoscopy. Actually, we have been very successful in obtaining biopsy specimens that showed carcinoma or tuberculosis when either was present. In a few cases of pancreatitis that we have examined by peritoneoscopy we have received a report of fat necrosis, which more or less clinched the diagnosis. I did not perform the peritoneoscopy in this patient; Dr. Serrano did. His preoperative diagnosis was tuberculosis or carcinoma.

DR. GUSTAV R. SERRANO: I cannot add much to what is in the record. There were only a few nodules, each not more than 3 mm. in diameter, one of which I am sure we got.

DR. CASTLEMAN: Dr. Ellis, you saw this patient; have you any comment?

DR. DANIEL S. ELLIS: I have been trying to remember her, but I am just as much in the dark as Dr. Harwood is at this point. I think I would have arrived at the same conclusion. It is possible that the patient could have had all this on the basis of cirrhosis, but I think that is unlikely in view of that peritoneoscopy. I believe that she probably did have carcinoma of the pancreas with enough involvement of the portal system to give her portal-vein block, varices and bleeding and that the liver enlargement was due to metastases or congestion.

CLINICAL DIAGNOSIS

?Carcinoma of body of pancreas.
Diffuse carcinomatosis.

DR. HARWOOD'S DIAGNOSES

Carcinoma of the pancreas, with involvement of portal vein and vena cava and with metastases to peritoneum.
Ascites.
Esophageal varices.
Splenomegaly.

ANATOMICAL DIAGNOSES

Scirrhous adenocarcinoma of pancreas, with pyloric, duodenal, transverse colon, portal vein and inferior vena cava obstruction and with metastases to regional retroperitoneal lymph nodes.
Esophageal varices with gastrointestinal hemorrhage, marked.
Hemorrhoidal varices.
Ascites.
Dilatation of stomach, marked.

Pathological Discussion

Dr. Castleman: Dr. Carlos Tejada, who performed this autopsy, has put a drawing of his findings on the board (Fig. 2). At the time of autopsy the abdominal cavity contained about 2 liters of clear straw-colored fluid. We could find no peritoneal nodules and no evidence of metastases. The striking finding concerned the stomach, which was tremendously distended and filled with over 6 liters of brownish-black turbid fluid. When this stomach was turned back, the gall bladder looked pretty normal. There was a huge mass, — 20 cm. in diameter, — in the retroperitoneal area (stippled in the drawing) that involved not only the head of the pancreas but the entire pancreas. The mass invaded the wall of the stomach at the pylorus, producing a narrowing there and another narrowing in the duodenum. It also pressed against the transverse colon, but nowhere did it invade the mucosa of the gastrointestinal tract. It almost completely occluded the splenic and portal veins, although we were able to pass a very narrow probe through the lumen, but there was no thrombosis. There certainly was enough compression of the portal vein to produce the enlarged spleen and the varices of the esophagus. One of the varices had ruptured and was the source of the dark-brown fluid found in the stomach and of the tarry stools we found below. The tumor also involved the inferior vena cava, producing considerable narrowing, which accounted for the marked peripheral edema.

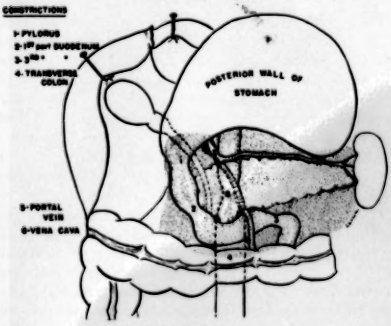

Figure 2.

At the time of autopsy there was no evidence of tumor anywhere else in the body, except in a few regional nodes along the pancreas. The cut section of the tumor was so hard and fibrous that we thought that it was possibly a fibrosarcoma of the pancreas. Although the common bile duct in the pancreas was narrowed, pressure on the gall bladder allowed bile to come through into the duodenum — evidence for the absence of jaundice. This also led me to believe it was not the usual sort of carcinoma of the pancreas, which would ordinarily produce jaundice with this degree of bile-duct narrowing.

Microscopically, most of the tumor was composed of dense fibrous tissue, in which was an occasional glandular space, usually perineurial in location (Fig. 3). The large regional lymph nodes showed an obvious adenocarcinoma. Thus we have a highly scirrhous adenocarcinoma that has been growing very slowly. In many fields one had to hunt to find tumor cells. So much of the tumor was within nerve sheaths that it is amazing that the patient had no pain. We often think that the involvement of nerves by carcinoma so often seen in carcinoma of the pancreas and the prostate is the cause of pain. If that was so, surely this patient should have had excruciating pain.

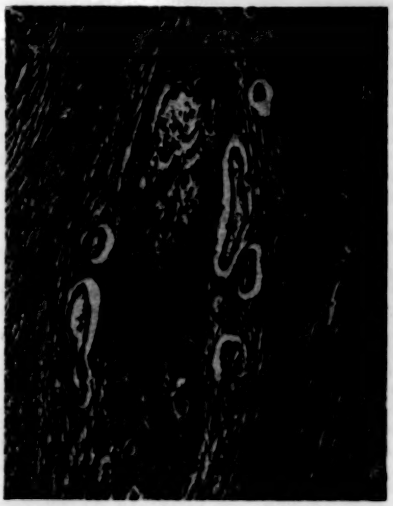

Figure 3. *Perineurial and Intraneurial Invasion by Adenocarcinoma.*

Dr. Earle M. Chapman: What did the thyroid show?

Dr. Castleman: A colloid goiter. The liver was quite normal.

Dr. Ellis: The protocol said it was enlarged, tender and 4 fingerbreadths below the costal margin.

Dr. Castleman: It weighed only 1200 gm. — rather smaller than usual. I wonder if the examiners were feeling the tumor mass, rather than the liver.

Dr. Ellis: If the liver was pushed up under the diaphragm, the physicians may have been feeling the dilated stomach.

CASE 37522

Presentation of Case

A fifty-nine-year-old man was admitted to the hospital because of hiccoughs and an x-ray shadow of a "mediastinal mass."

One month before admission the patient had a sudden onset of hiccoughs; these continued intermittently and usually were worse at night. Since treatment by drinking water, breath-holding, sedatives and rebreathing into a bag were ineffectual, three weeks prior to admission he entered another hospital. The inhalation of carbon dioxide resulted in a rapid but temporary subsidence of the hiccoughs, but it was of no avail when they recurred; intravenously given medication relieved the symptoms. The patient remained asymptomatic until one week before admission, when the hiccoughs recurred with more severity, and the paroxysms were associated with shortness of breath. An x-ray film of the chest showed a mediastinal mass. There was no cough, hemoptysis, chest pain, hoarseness, fever or weight loss. There was no diminution in strength or visual or speech disturbance. For the month prior to entry he had had intermittent bouts of nonbloody diarrhea.

A sister had asthma and a brother had died of consumption at the age of fifty.

Physical examination revealed an almond-sized lymph node in each axilla. The eyes were normal. The thyroid cartilage was markedly deviated to the right. The trachea was slightly deviated to the right and was movable. The venous pattern was prominent over the upper anterior chest wall. The nose, throat and larynx were normal. There was slight diminution of breath sounds over the right fourth intercostal space anteriorly. On percussion the area of cardiac dullness was found to extend 4.5 cm. to the right of the midsternal line in the third and the fourth intercostal space; the left border was normal in position. Grade I aortic and pulmonic systolic murmurs were heard, and the pulmonic second sound was louder than the aortic. The abdomen was negative. There was no clubbing of the fingers or toes. There was + pitting edema of the ankles. Rectal examination showed the prostate to be enlarged 1.5 times and firm and symmetrical. The left epididymis was enlarged, firm and translucent. Neurologic examination was negative.

The temperature was 99°F., the pulse 80 and the respirations 20. The blood pressure was 140 systolic, 90 diastolic.

A urinalysis was negative. Examination of the blood showed a white-cell count of 6400, with a normal differential, and a hemoglobin of 14.5 gm. A stool was guaiac negative. The serum protein was 6.05 gm., with a normal albumin-globulin ratio, the nonprotein nitrogen 28 mg. and the uric acid 4.6 mg. per 100 cc.; the blood chloride was 106 milliequiv. per liter. The prothrombin time was 22 seconds (normal, 17 seconds). A blood Hinton test was negative. An x-ray film of the chest showed an 8-cm. lobulated oblong nonpulsating mass in the right anterior mediastinum just below the carina; this was close to the right border of the heart and the ascending aorta (Fig. 1). The remainder of the lung fields were clear except for a calcified mass in the left lower lung field. Diaphragmatic motion was good. A film of the abdomen showed normal kidneys and some enlargement of the spleen.

Figure 1.

For several days the patient was free of hiccoughs, which then recurred; this time they were relieved by rigorous traction on the tongue. There was no diarrhea. On the eleventh hospital day an operation was performed.

Differential Diagnosis

Dr. F. Thomas Gephart*: In summary, this is a fifty-nine-year-old man who had hiccoughs and x-ray evidence of a mediastinal mass. I think, in view of that, it would be best to look at the x-ray films first.

Dr. Stanley M. Wyman: The only film we have, unfortunately, is this damaged one. There is a mass in the anterior mediastinum that bulges to the right of the midline and has a somewhat nodular or lobulated border (Fig. 1). It seems to lie far anteriorly. According to the fluoroscopist's report, it did not show any intrinsic pulsations. The spleen may be a little larger than usual, but I think that is a questionable observation.

*Assistant in surgery, Massachusetts General Hospital.

DR. GEPHART: Would you say the trachea was pushed aside?

DR. WYMAN: I think the trachea lies in approximately normal position

DR. GEPHART: There is no evidence of pleural effusion?

DR. WYMAN: No fluid and no evidence of intrinsic disease that can be localized.

DR. GEPHART: This case is unusual in that there was a mediastinal mass that was picked up because of a symptom — namely, the hiccoughing. Nowadays most mediastinal tumors are picked up by x-ray examination. I can dispose of the presenting symptom, the hiccoughing, by saying that it was apparently due to irritation of the phrenic nerve; certainly a mass in the right anterior mediastinum would press on or perhaps involve the right phrenic nerve. Incidentally, I think this case emphasizes the inefficacy of the numerous ways of treating hiccoughs. Apparently the patient ran the gamut.

It is almost impossible to tell definitely from the x-ray findings and physical examination what these mediastinal masses are in most cases. Of a series recently treated in this hospital the preoperative diagnosis was accurate in only 50 per cent of cases. This brings out that it is important to confirm the diagnosis by a more suitable kind of examination — namely, a thoracotomy.

In this case one ought to think of the vascular conditions that might cause this shadow. The two most likely possibilities are aneurysm of the sinus of Valsalva and pericardial cyst. The aneurysm of the sinus of Valsalva can be eliminated because there were no pulsations and no calcifications. A pericardial cyst cannot be completely eliminated, but because of the irregular shadow and the fact that no pulsations were seen at the time of bronchoscopy it is unlikely.

Was this a benign or a malignant lesion? Two things suggest, but are not diagnostic of, a malignant lesion: One is the assumed involvement of the phrenic nerve; the other is the prominence of the veins, particularly of those of the anterior upper chest, which may have been caused by compression on the vena cava. However, invasive or highly adherent dermoid cysts that are not actually malignant may present this type of picture.

In this region we can always expect metastatic disease from cancer elsewhere in the body. The translucent mass in the epididymis can, I think, be discarded; it probably was a small cyst and not a malignant lesion. There was a deviation of the thyroid cartilage but little evidence in the x-ray examination of the trachea's being deviated. I expect that the patient had an enlarged thyroid gland, but it was not mentioned in the physical examination. I bring that up because there is a possibility that the patient had a carcinoma of the thyroid gland with metastases to this region — or perhaps he had a carcinoma in a plunging goiter. This mass was somewhat low for a carcinoma in a plunging goiter, but we do see them on the diaphragm occasionally. Although the bloody diarrhea is something to think about, it had apparently cleared up by the time of admission and the stools were negative; I shall have to discard that as a possible source for cancer. I am unable to explain it.

One of the most common mediastinal masses is that caused by Hodgkin's lymphoma. That usually occurs around the hilum. This mass seems to have been well anterior, without any definite evidence of hilar involvement. It is also usually bilateral.

There are four groups of tumors that usually form masses in the anterior mediastinum: dermoid cysts, teratomas (there is some question whether these are a separate group, because sometimes a careful study of dermoid cysts will reveal that they are really teratomas), thymomas and simple, clear water cysts. Bronchogenic, tracheal and esophageal cysts usually occur in the middle lung field or near the hilum. Neurofibromas are usually posterior, although they may be anterior. Dr. Robbins[1] reports that 5 out of 14 neurofibromas that he studied were of the anterior variety.

I am going to have to make a diagnosis simply on the basis of statistics; on that basis I shall say that this was a dermoid cyst. There is a possibility, of course, that it may have been a thymoma or a simple cyst.

One thing I want to emphasize is that because of the difficulty in making a preoperative diagnosis one must make the diagnosis by biopsy or excision if possible. If it is a benign cyst, there is always the chance that it will become infected; if it is a benign solid tumor, there is a chance that it will become malignant.

DR. EDWARD B. BENEDICT: Is there any chance of this being a primary lung tumor?

DR. GEPHART: I cannot rule it out.

DR. BENEDICT: Can Dr. Wyman rule that out?

DR. WYMAN: No, but my first bet is a benign tumor, as was Dr. Gephart's. We have, however, seen bronchogenic carcinomas causing signs very similar to this.

DR. HELEN S. PITTMAN: This x-ray picture is very much like that of a tumor that I think was thymic in origin, a biopsy of which you examined a few weeks ago. That was of long duration and was also lobulated, but more adherent, perhaps; it was a benign thymic tumor.

CLINICAL DIAGNOSIS

Mediastinal tumor, ?lymphoma.

DR. GEPHART'S DIAGNOSIS

Dermoid cyst of anterior mediastinum.

ANATOMICAL DIAGNOSIS

Thymoma.

Pathological Discussion

Dr. Benjamin Castleman: The preoperative diagnosis was nonspecific, although the surgeons questioned the possibility of lymphoma. At operation the surgeon was unable to remove the large mass involving the mediastinum because he found that it had invaded the pericardium. A small biopsy was taken, which I shall show you. The striking finding in this slide is the two types of cells, lymphocytes and large epithelial cells, the combination of which is quite characteristic of the tumors primary in the thymus gland. We therefore made a diagnosis of thymoma. In some thymomas there is an even distribution of the two types of cells, but in most of them there is a preponderance of one. In this case there was a marked preponderance of lymphocytes. Because the tumor could not be removed the patient received x-ray treatment. This patient was operated on in 1947; I happened to discover his record when reviewing our cases of thymic tumors. After x-ray treatment the tumor completely disappeared, and the patient is very well now, four and a half years later. I shall ask Dr. Wyman to show the postoperative films.

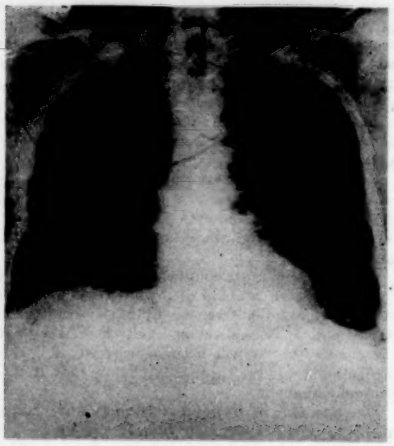

Figure 2.

Dr. Wyman: These two films, taken six months and four years postoperatively, demonstrate the startling change from the original examination (Fig. 2). The patient had considerable radiation reaction six months later that cleared up in the last film.

Dr. Castleman: In contrast to this case, we have just had a similar case of an inoperable thymoma in which the predominant cell was epithelial and there was no response to x-ray treatment.

Dr. Gephart: Are these malignant?

Dr. Castleman: Whether any thymic tumor should be called malignant is still questionable. They are malignant if you believe that an invasive tumor is malignant; they do not metastasize outside the chest. The thymic tumors associated with myasthenia gravis never have widespread metastases — merely local implantation or invasion within the chest. In our experience[2] and in the experience of the Mayo Clinic,[3] also, there has not been a thymoma, with or without myasthenia gravis, that has metastasized outside the chest. They may invade the pericardium, pleura or lung by extension; they may even implant on the diaphragm; but they do not go outside the chest. The tumors that do have widespread metastases will prove on careful evaluation to be tumors of the lung, lymphomas or metastatic tumors. If you want to define malignancy as a condition that spreads generally by metastasis outside its local areas, thymomas are not malignant, but they will be the cause of death by invading the vena cava, the phrenic nerve and other organs in the vicinity of the tumor.

Dr. Daniel S. Ellis: Did this cure the hiccoughs?

Dr. Castleman: The operation did not, but the x-ray treatment did.

Dr. Gephart: Do you find that some of the dermoid cysts have as much tendency to spread after a number of years as the thymic tumors? Frequently at operation there is so much reaction around a dermoid cyst that it is impossible to remove it.

Dr. Castleman: I personally have not seen dermoid cysts invade as the thymic tumors do.

Dr. Benedict: Did the circulation return to normal?

Dr. Castleman: Yes; the patient was seen just about one month ago in the Out Patient Department and seemed entirely well.

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Correction. In Case 37501 of the Case Records of the Massachusetts General Hospital, which appeared in the December 13 issue of the *Journal*, the second line of the legend for Figure 2, on page 944, should be changed to read "Note slight atherosclerosis" instead of "Note severe atherosclerosis."

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INSTITUTE OF WAR AND PEACE

WAR is perhaps the single greatest environmental force acting to disturb the ecologic equilibrium of man — that is to say, his adaptation to the world, its living organisms and his fellow man. The influence of environment as a cause of war is clearly demonstrated in the history of the great maritime powers, past and present — the Viking kingdoms, Genoa, Venice, Portugal, Spain, Holland and England. As a cause of peace it is clearly evident in the history of Switzerland and the Scandinavian countries.

Ecologic influences on the course and conduct of war have been recognized by all great strategists from Machiavelli through Von Clausewitz to the present. The title of the late Hans Zinsser's volume *Rats, Lice and History* is a thumbnail definition of war placed in its proper context as a part of natural history. The great Russian surgeon of the past century, Pirogoff, defined war as an "epidemic of trauma." The occurrence of infectious hepatitis at Gallipoli during World War I and of trench foot at Attu, Caserno and Bastogne during the Second World War are striking illustrations of ecologic action on the results of a campaign.

If it is accepted that war and famine are as much a concern of community health as pestilence and that public health is merely the application of medical ecology to social uses, certain consequences follow about which the nation and its leaders, — medical as well as political and military, — should be thinking. These consequences concern the future direction of public-health activity and its effect on aging, nutrition, overcrowding and the rivalries of national and world populations. Our failure to date to study the ecology of man accounts to a large degree for the failure of diplomats to undo all the mischief piled up for them by war lords, well-meaning scientists, and Nature herself. From Machiavelli's time on, astute leaders have studied how to apply science to remedy a social crisis — but have not studied enough how to prevent one prior to the explosion that signals the outbreak of war.

In the first quarter of the sixteenth century Machiavelli wrote that "a prince ought to direct all his thoughts and facilities in the direction of war. . . and in his warlike operations. . .must be more assiduous in times of peace than in those of war." Now, more than five centuries after *The Prince* was penned, man is gradually coming to study war the way he does agriculture — a science devoted not only to the relief of famine but to its prevention. If a Russian has come to the conclusion that war is an "epidemic of trauma," perhaps the phenomenon should be studied as an epidemic, like automobile accidents and the Donora Smog. Perhaps a Point 4 program is not enough — perhaps international issues should include 5 or 10 basic points.

Whatever the theoretical basis, Columbia University, under the stimulus of General Eisenhower's leadership, has established an Institute of War and Peace Studies. Members of the institute will in-

vestigate war, — scientifically, it is to be hoped, — "as a method of protecting values considered even more precious than the values which war places in jeopardy" and will attempt to find "less costly ways of protecting those things for which we are willing to fight."

The season between Christmastide and New Year's Day is a peculiarly fitting one in which to get under way, with the "Godspeed" of the world ringing behind it.

PROTECTION AGAINST EPIDEMIC (INFECTIOUS) HEPATITIS WITH GAMMA GLOBULIN

THE high incidence of infectious hepatitis in our armed forces in Korea and the frequency with which it is now occurring among civilians in this vicinity have aroused new interest in the value of gamma globulin in the prevention or possible attenuation of this disease. Early in 1945 Stokes and Neefe[1] reported the results of the intramuscular injection of gamma globulin in exposed persons during an epidemic of infectious hepatitis that occurred in the previous summer in a camp for boys and girls. They chose an arbitrary dose of 0.15 cc. per pound of body weight. Their results were comparable to those observed after similar injections of gamma globulin in susceptible persons exposed to measles; they indicated that gamma globulin is capable of preventing or attenuating infectious hepatitis when administered to exposed persons during the incubation period of the disease.

Although these data suggested that the best results were obtained when the globulin was injected early in the incubation period, it seemed possible that, as in measles, it may also be of therapeutic value early in the preicteric stage of hepatitis. The results seemed sufficiently encouraging to warrant further trials of gamma globulin in the control of other epidemics of the disease, since no other effective control measures have been developed.

Reports of such trials were soon forthcoming. Gellis and others[2] conducted field studies on the effect of human gamma globulin in the course of a severe epidemic of infectious hepatitis that occurred during the fall of 1944 and the following winter in the Mediterranean Theater of Operations in a heavy-bombardment group and in various regiments of ground forces. In this study a uniform dose of 10 cc. was administered to each patient; this amounted, on the average, to about 0.06 cc. per pound of body weight. In three groups of cases that they studied, infectious hepatitis with jaundice was found to be about six times as frequent in control subjects as in those in the same unit who had been inoculated with gamma globulin. The results of these studies supported the findings of Stokes and Neefe that gamma globulin was a potent agent in the prevention of infectious hepatitis and suggested that the passive immunity so conferred lasted at least six to eight weeks.

A parallel study was also carried out by Gellis and his co-workers[3] to determine the effect of gamma globulin on the course of infectious hepatitis when given in the early preicteric stage of the disease. In that study the dose was 0.3 cc. per pound of body weight, but no evidence was obtained in favor of an attenuating effect of the gamma globulin when administered in this manner early in the course of the disease.

Another prophylactic study, carried out during an institutional outbreak, was reported at the same time by Havens and Paul.[4] In this study the case rate of hepatitis with jaundice in the controls was about 10 times that noted among those who received the prophylactic inoculations of gamma globulin. The average dose used by Havens and Paul was 0.08 cc. per pound of body weight; this seemed to be about as effective as the dose of 0.15 cc. per pound originally used by Stokes and Neefe.

More recently, Stokes and his co-workers[5] carried out further prophylactic studies during three epidemics in well segregated institutions. The latest studies were designed to determine whether recent batches of gamma globulin were as effective as the batches first used; whether smaller doses could be used as effectively as the larger ones; and how long protection by gamma globulin remained when the exposed persons who had been inoculated continued to be exposed to the disease.

These latest studies indicated that gamma globulin of recent batches is highly protective in passive immunization against viral hepatitis. In one institution in which different dosages were studied

there was clear-cut evidence that as small a dose as 0.01 cc. of globulin per pound of body weight gave protection. A single injection of globulin used in each of the three institutions caused protection of the inoculated groups for at least five, nine and eight months, respectively, despite their continued intimate exposure to continuing cases of hepatitis in the control groups.

From these results it was considered most likely that the waning passive immunity induced by the gamma globulin afforded the opportunity for inapparent or subclinical infections among the inoculated group, which then resulted in active immunity superimposed on the passive immunity. The results of animal viral studies, in litters born to immune mothers and exposed to natural virus, were interpreted as compatible with such an explanation. The authors suggested other possible uses of so-called "passive-active" immunization in viral diseases both in the newborn period and during childhood, in either the presence or the absence of epidemics, by means of injection of immune bodies.

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2. Gellis, S. S., et al. Use of human immune serum globulin (gamma globulin) in infectious (epidemic) hepatitis in Mediterranean Theater of Operations: studies on prophylaxis in two epidemics of infectious hepatitis. *J. A. M. A.* **128**:1062, 1945.
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4. Havens, W. P., Jr., and Paul, J. R. Prevention of infectious hepatitis with gamma globulin. *J. A. M. A.* **129**:270-272, 1945.
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THE COMMONWEALTH FUND REPORTS

Generally speaking, annual reports are among the driest reading encountered from one year's end to another. Not so, however, with the annual report of the Commonwealth Fund; it has always been well written, and the report for the year ending June 30, 1951, is no exception.

For a long period the Commonwealth Fund has observed medical education from a seat behind the bench; its observations thus have depth and perspective. Signs of another turning point are multiplying, the Fund reports:

> In spite of progress already made many medical schools are dissatisfied with the teaching they are now doing. The points at which change is desirable and possible begin to be clearer. Medical educators are asking such questions as "whether the right people are now coming to medical school, how students should be chosen and what educational experience they should have before they enter it; how medical teaching can build on what the student brings with him; how the medical sciences can be woven together and related to the patient; how the break between "scientific" and "clinical" courses can be closed; in a word, how the learning process can become continuous and coherent.

The largest grant made for the purpose of helping a medical school to find answers to some of these questions went to Cornell, to support, for a three-year period, a new clinic for "comprehensive medical care in the outpatient department of the New York Hospital, to which medical students will be assigned for half their senior year." During these four months the student will receive parallel instruction in medicine, pediatrics and psychiatry; it is hoped that the student, by repeatedly seeing the same patients, will obtain a better idea of health and sickness. This takes into consideration the fact that it takes time for most persons to become acquainted with one another. It is a very small beginning of the correction of a trend that has undoubtedly become one of the most awkward aspects of medical education. Today many schools give courses not only in the basic sciences but additionally in "applied basic sciences," not only in laboratories but in "laboratory medicine" and not only in public health but in "preventive medicine." It is hard to believe that such fragmentation is helpful to the students.

Another large grant was made to the University of Colorado, also for a three-year experiment — intended "to demonstrate the practice of good general medicine," which this medical school is said to emphasize in its teaching. At the Denver General Hospital, another of the large city institutions used for teaching purposes in this country,

> A general medical clinic staffed by graduate students of medicine preparing for general practice, aided by juniors and seniors from the medical school, will be the center from which a broad program of medical care in the home, clinic, and hospital will be provided for Denver indigents. . . . Here, under the supervision of a staff in which general and specialty training are carefully balanced, graduate and undergraduate students will have consecutive experience in the care of patients for at least two years.

Other grants include one to the Department of Rehabilitation and Physical Medicine of New York University College of Medicine and to a psychiatric

teaching program at the University of Cincinnati. Support will be continued for a regional postgraduate educational service carried on by the two medical schools in Virginia. The Fund will also contribute to the cost of training medical scientists for research at the Massachusetts Institute of Technology for the next five years and will help in the development of field training at the Harvard School of Public Health. Appropriations for experimental health services will include an "intensive study of family experience with medical care under the Health Insurance Plan of Greater New York and in a comparable sample of New York families outside that plan."

It is of interest to learn that the former Harkness residence at 1 East 75th Street, New York City, has been given to the Commonwealth Fund and is being altered for occupancy as headquarters for the Fund's future operations. This is certainly an appropriate and useful disposition of property that might otherwise become, in these changing times, a real-estate problem.

POLITICAL ECONOMY?

THE residents of various populous parts of the country will be pleased to learn that mink coats may eventually decrease in cost, if not in desirability. This situation, fraught as it is with implications of a social and political nature, has been brought about by the researches of a leading pharmaceutical firm, which have resulted in the development of a vaccine to prevent distemper in minks.

Mink distemper, the virus of which was recognized in 1932, has been one of the major hazards of mink-ranching, killing annually thousands of the animals whose name has been a byword in those areas where gifts to warm the sometimes chillier sex have been in vogue.

Under ordinary circumstances the disease entails a death rate of 60 to 100 per cent, and the pelts of survivors are usually of inferior quality. Vaccines in use at the present time require a series of inoculations and confer a relatively short immunity, whereas a single injection of the new vaccine immunizes for a year, or four months beyond the age at which the pelts are ordinarily harvested.

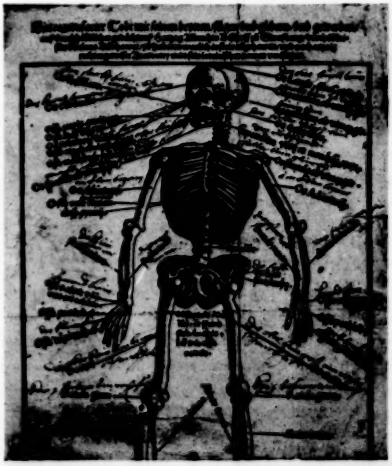
Dr. C. P. Johnson, professor in Hampden Sidney Medical College, Va., says in the Stethoscope *that a mixture of vinegar and salt, two parts of the former and one of the latter, a table-spoonful every three hours, has been found very useful in obstinate diarrhoeas.*

Boston M. & S. J. *December 31, 1851*

BOSTON MEDICAL LIBRARY

THE WECHTLIN SKELETON

The broadside of a skeleton here reproduced was drawn and engraved about 1517 by Hans Wechtlin of Basle, a noted engraver. He was called "the master with the crossed pilgrim's staves," because he used this design as his monogram. The Latin names of the bones are printed, and in most cases a German translation has been written by an unknown person. Unfortunately, the copy acquired by the Boston Medical Library is defective, lacking the depiction of the feet.



Choulant,[1] in his scholarly analysis of early anatomic illustration, discusses at length the depiction of skeletons in early manuscripts; his book reproduces the Helain broadside of 1493, which is the first printed depiction of a skeleton and of which only one copy is known.

The next advanced step was the Grüninger[2] skeleton of 1497, named for the publisher of Hieronymus of Brunschwig's book on surgery.

The Wechtlin[3] skeleton is much further advanced in accuracy, particularly in the drawing of the skull, the vertebras and the long bones. This drawing was almost immediately reproduced in the surgical handbook of Gersdorff[4] and in the medical treatise of Phries[5] as large folding plates. The heading of the Gersdorff plate is different from that of the Wechtlin; there are also two columns of verse at the bottom of the Gersdorff plate. The Phries plate has no heading and is a plain case of misappropriation.

References

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2. Von Brunschwig, H. *Das Buch der Cirurgia.* Strassburg, 1497. In *Von der Anathomia,* a supplement found in some copies of the first edition.
3. Wechtlin, H. *Ein contrafacter Todt mit seinen beynen Fuegen und Gliedern und Gewerben. . .in Stein abgehawen und nach anzaig/ rechter gewiser Anatomey mit sein latinischen Namen verfüciert.* Basle, 1517.
4. Gersdorff, H. *Feldtbuch der Wundtartzney.* Strassburg, 1517.
5. Phries, Phyrysen, or Fries, L. *Spiegel der Artzney des gleichen Normals.* Strassburg, 1518.

(All books mentioned are in the Boston Medical Library.)

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

THE PHYSICIAN'S RESPONSIBILITY IN MASSACHUSETTS CIVIL-DEFENSE ORGANIZATION*

VLADO A. GETTING, M.D., DR.P.H.†

Federal Civil Defense Administration

Our national civil-defense organization is developed by the Federal Civil Defense Administration directed by former governor of Florida Millard F. Caldwell. Created by an act of Congress in 1950 (Public Law 920), the Federal Civil Defense Administration has assigned the responsibilities for medical and health services to Col. William L. Wilson, M.C., United States Army, Assistant Administrator for Health and Welfare. Under his direction Dr. Norvin C. Kiefer is Chief of the Health Services and Special Weapons Division and as such is responsible for the development of the health policies and procedures of the national civil-defense program. These policies have been formulated in the official document AG 11-1 entitled "Health Services and Special Weapons Defense," which serves as a foundation on which state and local civil-defense activities are developed. From time to time the Federal Civil Defense Administration plans to publish bulletins that will serve as recommendations or directives to states and communities for the development of their programs. The regional office serving this section of the United States is headed by Mr. A. D. O'Connor, whose headquarters are in the Federal Building in Boston. The district medical director of the Public Health Service, Dr. Richard Boyd, is temporarily acting as the medical director for the regional office of the Federal Civil Defense Administration. The objectives of the regional offices are to assist states with advice and consultation in the development of their own state programs and for the co-ordinating and developing of interstate agreements.

*Presented at the annual meeting of the Massachusetts Medical Society, Boston, May 24, 1951.

†Massachusetts Commissioner of Public Health.

State Organization

The Commonwealth Disaster Organization was revitalized by the passage of Chapter 639 of the Acts of 1950, which replaced the former disaster organization by a new civil-defense agency directly responsible to the Governor and under the leadership of a director appointed by him. A defense council appointed by the Governor acts in an advisory capacity to the Governor and the director. Among the physicians appointed to this council are Dr. Leland S. McKittrick, Dr. Norbert A. Wilhelm and Dr. Clarence L. Scamman.

The State Civil Defense Agency is under the direction of Mr. John Stokes, formerly Commissioner of Public Safety. It is divided into seven major divisions, each of which is administered by a head of an existing department of the Commonwealth. These divisions, in accordance with the Act, utilize existing agencies to the fullest extent possible and enlist the assistance of numerous volunteers.

The divisions are:

Medical and Health, under the direction of the Commissioner of Public Health, Dr. Vlado A. Getting
Rescue, Transportation and Evacuation, under the direction of the Commissioner of Public Works, William F. Callahan
Police, under the direction of the Commissioner of Public Safety, Daniel I. Murphy
Fire, under the direction of the State Fire Marshal, Edward P. Gilgun
Communications, under the direction of the Commissioner of Public Safety, Daniel I. Murphy
Utilities, under the direction of the chairman of the department of Public Utilities, Thomas A. Flaherty
Civilian War Aid, under the direction of the Commissioner of Public Welfare, Patrick A. Tompkins

In the event that an emergency may occur, the headquarters of the State Civil Defense Agency will be located at the State Police Training School in Framingham.

For administrative purposes, the State has been divided into nine civil-defense regions, each of which bears a designated number and has as its director the chief executive of the largest community within the region. Thus, Mayor Hynes of Boston is director of Region V, which includes the Metropolitan area. Within each of the nine regions there is a reduplication of the seven major divisions existing in the State organization.

Each of the 351 municipalities in the Commonwealth is required by law and by executive order of the Governor to develop its own civil-defense organization and to provide insofar as practicable the various essential services for disaster relief.

Medical and Health Division of State Civil Defense Agency

In accordance with the recommendation of the Federal Civil Defense Administration, the State Department of Public Health forms the nucleus of the Medical and Health Division of the State Civil Defense Agency. By law all state departments are required to give such assistance as may be necessary in the development of the organization and the implementation of the program. The Medical and Health Division consists of twelve major sections, each headed by a volunteer and assisted by one or more full-time employees of the Commonwealth. Although the Commissioner of Public Health is the official Head of the Medical and Health Division, the many responsibilities placed on him by law have made it necessary to appoint an executive officer, Dr. Robert E. Kelley, retired Captain, Medical Corps, United States Navy, to develop the medical and health program for civil defense. Because of his experience, both clinical and administrative, in the navy and his actual experience in Pearl Harbor during the bombing of that port by the Japanese and because of his experience in public-health administration in Massachusetts as district health officer for the Department of Public Health in Metropolitan Boston, he is admirably suited to the responsibilities of this position.

The Medical and Health Division has an advisory committee comprised of physicians, dentists, veterinarians, pharmacists, undertakers, nurses, engineers, physicists, nutritionists, supply experts, chemists and other specialists. Each of the sections has not only a chief but one or more associates and assistant chiefs, as well as an advisory committee, all appointed on recommendation of the chief of the section.

The function of the State Civil Defense Agency is to assist municipalities in the development of their programs, as the local civil-defense organization will be the basic operational unit in times of emergency. Should a catastrophe exhaust the facilities of a community or a group of communities that have formed a mutual-aid pact, the regional office and, in turn if necessary, the State Civil Defense Organization may be called on to take charge and request assistance from other regions and other states in accordance with prearranged plans and agreements.

Thus, the Medical and Health Division of the State Civil Defense Agency is responsible for the over-all planning, which should be implemented by the municipal and regional offices as far as their resources permit.

The development of the plan of operations in any municipality such as Boston or Wellesley is the responsibility of the head of the Medical and Health Division of the municipal civil-defense agency. The State will assist in the formulation of over-all standard procedures and plans in accordance with such standards and policies as are developed by the Federal and State Governments. In times of emergency the head of the Medical and Health Division of the State Civil Defense Agency and his staff of section chiefs and their assistants would report to the Framingham headquarters for the purpose of co-ordinating operations to meet the needs for disaster relief.

First Aid and Ambulance Section

Since the prime responsibility in disaster is the care of the injured, this responsibility is assigned to the First Aid and Ambulance Section, whose chief is Dr. Brooks Ryder. In accordance with the recommendations of the Federal Civil Defense Administration, the state is planning the development of one first-aid station for each 10,000 population, or approximately 500 first-aid stations in the entire State. The personnel for each first-aid unit will consist of two physicians, three dentists, three nurses, two pharmacists, fifteen first-aid workers and nurses' aides, six clerical assistants and 150 litter bearers and ambulance personnel. Each team of 196 persons will assemble at a prescribed place and will be transported in assigned vehicles, together with equipment, to a selected site to set up its first-aid station. Located in churches or public schools, the first-aid stations will encircle an area with a 1½-mile radius about ground zero of an atomic bomb burst. This ring of fifty-seven first-aid stations at 1/6-mile intervals will be surrounded by a second ring of thirty-nine first-aid stations 1/3 of a mile apart about 2 miles from ground zero. Thus the ninety-six first-aid stations will be able to handle the estimated 60,000 casualties that will result from a single atomic bomb burst of the Hiroshima type. Realistic estimates of the number of wounded in relation to the actual density of population in Boston and other primary targets in the Commonwealth are now in preparation. Such estimates will also take into consideration the use of larger atom bombs and the simultaneous utilization of other weapons. It is expected that over some primary targets an attack would take place by a squadron of planes, one or more carrying atomic bombs and the rest of the squadron carrying other types of weapons, such as bombs filled with chemical or biologic agents or incendiary and demolition bombs. It is believed that Metropolitan Boston must be prepared for a surprise attack of a minimum of two atomic bomb bursts together with the simultaneous ultilization of other weapons.

Only three moves of the casualties are anticipated. Casualties will be picked up by the litter

bearers and transported to the first-aid station. Litter bearers and personnel at first-aid stations and casualty hospitals will have to utilize standard treatment within the limitations of the supplies and equipment available. Triage, or classification of patients for treatment, will be the responsibility of the physicians in charge of the first-aid stations and at the casualty hospitals. Because of the large number of injuries and the limited personnel and supplies available, it will not be possible for a physician to treat every patient or to use the treatment of his choice. Burn dressings consisting of dry compresses will be applied with moderate pressure, not by doctors but by litter bearers and others who have had training in first aid.

Ambulances will consist of converted trucks and busses specially equipped for this purpose. If further treatment is indicated, the casualties will be transported from the first-aid station to the casualty hospital. From the casualty hospital patients will be discharged home, to other housing facilities or to reserve hospitals for continued treatment if necessary.

Hospital and Medical Section

The visualized attack on Boston or any other primary target area would destroy most of the existing hospitals or render them inoperative because of structural damage. The lack of utilities in the fringe or perimeter area would make other hospitals partially inoperative, particularly if the attack occurred in winter. Broken windows and falling débris might be a problem as far as 10 to 12 miles from ground zero. Therefore, the development of converted hospitals, each capable of handling a minimum of 200 casualties, has been assigned to Dr. Charles G. Hayden, chief of the Medical and Hospital Section, and his associates, Dr. Nathaniel W. Faxon (responsible for the hospital organization) and Dr. Harold M. Frost (associate in charge of the medical organization). Each hospital must, in anticipation of disaster, formulate its own disaster program. Each person on the staff of a hospital must be trained, as must be the members of the first-aid team, until they can perform their duties under the most trying conditions. Existing hospitals must plan to increase their capacity to the fullest extent to handle casualties. Dormitory facilities such as nurses' homes, auditoriums, classrooms and neighboring buildings that are suitable for this purpose should be surveyed with a view to being converted into hospital facilities. In addition, many hospitals will be asked to organize complete hospital cadres consisting of physicians, nurses and ancillary personnel to staff converted hospitals that will be set up in appropriate buildings, such as schools and public halls. It has been estimated by Dr. Faxon and his associates that 50 per cent of the casualties will arrive at the hospitals during the first twenty-four hours, 40 per cent during the second twenty-four hours and 10 per cent during the third twenty-four hours. Later, as radiation illness develops, a second wave of casualties will enter the hospital. Special facilities for the care of complicated cases will have to be set up in reserve hospitals beyond the danger area. For example, there will be need for special teams to handle brain surgery and injuries of the head, chest and abdomen.

It is expected that hospitals will not be evacuated in advance of a bomb burst. The complexity and expense of permanently operating such large hospitals as the Massachusetts General, the Massachusetts Memorial and the Boston City hospitals in primitive or inadequate physical plants located beyond the target limits is impractical and unnecessary. Whenever an alert is sounded, hospital patients and personnel will be moved to places of safety within the hospital.

In addition to the responsibility for the care of casualties, the Hospital and Medical Section is charged with the medical care of evacuees. Special problems are the care of pregnant women who may have premature deliveries and miscarriages, the provision of delivery services, the care of premature infants and pediatric care for children. Mobile teams of physicians will be assigned to each evacuation point and reception station and to the temporary housing facilities for the care of these special medical problems.

Blood Section

Under the capable direction of the chief of the Blood Section, Dr. Lamar Soutter, methods are being developed by his associates and advisory committee for the blood grouping of a limited pool of donors in anticipation of the emergency. Thus far $15,000 has been appropriated by the General Court for the training of teachers who in turn will instruct typing technicians and also conduct a pilot program. It is expected that further appropriations will be made in order to meet the recommendations made by the Federal Civil Defense Administration that 150,000 persons be grouped on the basis of each 40,000 anticipated casualties that will survive twenty-four hours after the bombing. Such grouping will have to be made in regions immediately surrounding the expected ground zero and each potential donor will have to be identified properly, since it is expected that in the immediate hours after a catastrophe only Group O blood will be used. Shortly thereafter it is expected that laboratories will be able to blood-group and type recipients to make possible the utilization of other types of blood. Preparations are under way for stockpiling of plasma and other blood fractions, and all hospitals have been asked to stockpile liquid blood plasma. A request has been made for an appropriation to permit stockpiling of recipient and donor sets and blood bottles for the hours immediately following a catastrophe.

Laboratory Section

Dr. Geoffrey Edsall, chief of the Laboratory Section, and his staff have been preparing, together with the chiefs of other sections, plans for the formulation of the necessary laboratory services that will be required by the several sections. It is expected that existing laboratory facilities will be used whenever possible and their facilities supplemented wherever there is need. Mobile laboratories are being planned to provide services for special problems created by destruction of existing laboratories or the use of special weapons.

Vital Statistics

The Secretary of State and the Registrar of Vital Statistics have been requested to develop the plans for the recording of the necessary data. Thus far little has been accomplished in this direction.

Mortuary Section

Dr. Richard Ford, chief of the Mortuary Section, in conjunction with medical examiners and morticians, is developing plans for the handling of the dead. It is expected that immediately after a bomb burst there may be as many as 20,000 casualties, with a similar number dying in the first week. Proper identification of the cause of death as well as of the body and place of interment of each is necessary. A standard mortuary tag has been developed by the Federal Civil Defense Administration and is now under review by State Civil Defense medical officers.

Communicable Diseases Control Section

The chief of the Communicable Diseases Control Section, Dr. Conrad Wesselhoeft, his associate, Dr. John Snyder, and their staff are developing plans for the handling of large numbers of communicable disease cases that may occur as a result of breakdown of environmental sanitation and housing facilities. With the mass movement of populations it becomes vitally urgent that physicians report the occurrence of all cases of communicable diseases as soon as they are suspected. Since biologic agents may be used by the enemy, this section is also charged with the responsibility for early detection and epidemiologic investigations and such controls as may be indicated.

Monitor Section

Mr. Worthen Taylor is the engineer in charge of the Monitor Section and has the advice of medical consultants. Special advisers are Dean John Bunker and Professor William H. Radford, both of Massachusetts Institute of Technology. This division is responsible for training the teams to evaluate data concerning the possible residual radioactivity that may remain after an atomic-bomb explosion. The danger of radiation has been overemphasized in most of the literature; it is anticipated that only about 15 per cent of casualties would suffer from radiation illness after an air burst.

Chemical Weapons Defense Section

Dr. James L. Whittenberger, chief of the unit, is responsible for developing necessary teams for the detecting and delineation of areas that may be involved in chemical-weapons warfare.

Environmental Sanitation Section

Mr. Clarence Sterling, Deputy Commissioner of the Massachusetts Department of Public Health, is chief of the Environmental Sanitation Section and is responsible for supervising water supplies, disposal of sewage and human waste, sanitation of housing facilities and control of rodents and insects that may be a hazard under these conditions.

Food and Nutrition Section

Although the procurement and distribution of food is the responsibility of the Division of Civilian War Aid, the Health and Medical Division is responsible for the safety and nutritional aspects of food supplies through the Section on Food and Nutrition, under its chief, Dr. Fredrick Stare. Special teams of inspectors will have to be trained to supplement inspectors now available in local health departments to make the necessary sanitary inspection of food, particularly when food for evacuees is prepared under primitive conditions. Because some persons may remain in such housing facilities for long periods of time and because of the disruption of transportation and usual supplies, the choice and availability of food will be limited. This section is further charged with the development of an adequate program to assure that malnutrition does not become a major problem, as it did at Hiroshima and Nagasaki. It is the conviction of many that with proper nutrition many of the deaths and complications of infections in these Japanese attacks could have been prevented.

Health Supplies Section

The chief of this section is Mr. L. C. Adams, who is responsible for the procurement of drugs and equipment required by first-aid stations and hospitals and by those physicians who may be assigned to the care of evacuees. A request is being made for an appropriation to stockpile antibiotics, which will be required in large quantities, not only for the casualties resulting from mechanical injuries and burns but also as a defense against biologic weapons.

Conclusion

The Massachusetts Civil Defense Organization is progressing in its plans and organization. Considerable variations occur in the progress of organizations in the various municipalities. In the near future it is anticipated that the Federal Government will

appropriate money on a 50 per cent matching basis for the purchase of standard equipment and for some supplies for first-aid stations in the critical target areas. Appropriations are being requested from the General Court to meet the necessary matching requirements to obtain such supplies and for additional supplies and equipment that will be required. It is expected that approximately 750,000 persons will have to be blood-typed in Massachusetts at an expense of approximately $0.50 per person. Plans are being drawn for the building of a second story of the blood-laboratory building for the processing of plasma. Physicians may soon be expected to form hospital units or to participate in first-aid teams. It is expected that the Federal Government will stockpile hospital equipment and supplies in such localities that these would be available in about four hours after an attack.

All in all, the physician is faced with new responsibilities in the preparation for civil defense. He will have to play an intricate part in his community's civil-defense organization as a member of a team using standard methods, technics and supplies. He will be expected to triage patients, to devote his time to the care of the injured and to assign the care of his own family to other responsible persons in his household or neighborhood. In anticipation of disaster he will take part in training courses for physicians and in turn participate in the training of nurses' aides, and auxiliary personnel for first aid, home nursing and other duties. He will participate in the development of the first-aid unit and the evolution of the hospital casualty organization and must plan to take his particular assignment in the community-service planning of medical care of evacuees.

During the actual emergency the physician can expect to be entirely divorced from his household, to be called to duty under the various civil-defense rules and regulations and to take his assigned part in the organization.

Some physicians may be so engaged for weeks; others, for months. Rebuilding of a metropolitan area after destruction by atomic and incendiary bombs will take months and years. The physician, therefore, has not only an important role in planning and training for civil defense but a very important role during the actual emergency and thereafter. His willingness and readiness to serve under these trying circumstances and under conditions to which he is not accustomed will be the measure by which the American people will determine the physician's status in his community. The success of any disaster program is dependent on the whole-hearted co-operation of all. The doctor, individually and through his medical societies, has an important place on the civil defense team; he must fill it effectively and willingly.

Bibliography

United States Civil Defense. 165 pp. Washington, D. C.: Government Printing Office, 1950.

Health Services and Special Weapons Defense. (AG-11-1.) 260 pp. Washington, D. C.: Government Printing Office, December, 1950.

An Act to Authorize a Federal Civil Defense Program and for Other Purposes. Public Law 920. (81st Congress.) January 12, 1951. 14 pp.

An Act to Provide for the Safety of the Commonwealth during the Existence of an Emergency Resulting from Disaster or from Hostile Action. Chapter 639. (Massachusetts.) July 20, 1950. 13pp.

Civil Defense Supplement to the American Red Cross Textbook. Washington, D. C.: National Red Cross, January, 1951.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Clinical Unipolar Electrocardiography. By Bernard S. Lipman, M.D., assistant in medicine, Emory University School of Medicine, and Edward Massie, M.D., assistant professor of clinical medicine, Washington University School of Medicine, director of Heart Station, Barnes Hospital, St. Louis, and director, Cardiovascular Clinic, Washington University Clinics. 8°, cloth, 232 pp., with 191 illustrations. Chicago: The Year Book Publishers, Incorporated, 1951. $5.00.

This simple, practical manual is intended principally for the inexperienced in the field of "V-lead" electrocardiography. There are 64 pages of illustrative unipolar electrocardiograms, following the text proper. A bibliography of 219 titles and an index conclude the book. The publishing is well done.

Roentgen Manifestations of Pancreatic Disease. By Maxwell H. Poppel, M.D., associate professor of clinical radiology, New York University–Bellevue Medical Center, associate roentgenologist, New York University Hospital, associate radiologist, Mount Sinai Hospital, roentgenologist, Welfare Island Dispensary, New York City, consultant in radiology, United States Naval Hospital, St. Albans, Long Island, New York, attending consultant in radiology, United States Veterans Administration Hospital, Bronx, New York, and Commander (Medical Corps), United States Naval Reserve. 8°, cloth, 389 pp., with 166 illustrations. Springfield, Illinois: Charles C Thomas, 1951. $10.50.

This new book is essentially an x-ray atlas of primary diseases and secondary conditions of the pancreas. The first chapters deal with the anatomy of the pancreas and duodenum and roentgen methods of examination. These are followed by chapters on calcareous diseases, primary tumors and infections of the pancreas, pancreatic (exocrine) insufficiency, lesions of the pancreas of secondary origin, differential diagnosis and statistics. There is a bibliography of 295 references and a good index. The publishing is excellent, and the book should be in all collections on the subject.

Principles and Practice of Obstetrics (Originally by Joseph B. DeLee, M.D.). By J. P. Greenhill, M.D., attending obstetrician and gynecologist, Michael Reese Hospital, obstetrician and gynecologist, associate staff, the Chicago Lying-in Hospital, attending gynecologist, Cook County Hospital, and professor of gynecology, Cook County Graduate School of Medicine. Tenth edition. 4°, cloth, 1020 pp., with 1140 illustrations. Philadelphia: W. B. Saunders Company, 1951. $12.00.

This tenth edition of the original DeLee textbook has been almost completely rewritten by Dr. Greenhill to bring the text up to date, after consultation with three other authors concerning obstetrics, uniformity in certain definitions, terms, classifications and procedures. The author had the assistance of a number of physicians in writing on special subjects. Much new material has been added. Many of the old illustrations have been deleted and many redrawn; 151 new ones have been added. Bibliographies have been appended to the various chapters. A comprehensive index concludes the text. The publishing of this standard textbook is excellent. It should be in all reference collections on the subject.

A History of Neurological Surgery. Edited by A. Earl Walker, M.D., professor of neurological surgery, Johns Hopkins University School of Medicine. 4°, cloth, 583 pp., with 152 illustrations. Baltimore: The Williams and Wilkins Company, 1951. $12.00.

This special history is based on a seminar given by the members of the Division of Neurological Surgery of Johns Hopkins University School of Medicine during the winter of 1949-1950. The original papers have been revised and critically examined by a number of historians and neurosurgeons. There are 16 chapters, a prologue and an epilogue, covering the whole field of neurosurgery. The prologue presents the history of trepanation from the time of prehistoric man through the Greco-Roman period, and the development of neurology and surgery in the modern period. The text is concluded with a bibliography of 2371 references, arranged alphabetically by author. Places of publication of the various periodicals cited are with a few exceptions omitted. This omission is to be regretted, as this history will have a worldwide reading public to whom many of the periodicals will be unknown. The monumental work of Osborne on men of the Old Stone Age seems to have been missed. The practice of modern cataloguers is to put the old Latin forms of place names into the vernacular. There is a good combined index of authors and subjects. The publishing is excellent. The book should be in all medical libraries and in all collections on neurology and surgery.

Post-Graduate Lectures on Orthopedic Diagnosis and Indications. Volume II. By Arthur Steindler, M.D., professor of orthopedic surgery, State University of Iowa College of Medicine. 4°, cloth, 198 pp., with 140 illustrations. Springfield, Illinois: Charles C Thomas, 1951. $6.00.

Section A of Dr. Steindler's book discusses paralytic disabilities — poliomyelitis, paralytic scolioses and spastic paralysis. Section B covers static disabilities — lumbosacralgia, or low-back pain, and the intervertebral disk, idiopathic scoliosis, internal derangement of the knee joint and static deformities of the foot and ankle. To each chapter is appended a list of selected references. There is a good index and the book is well published. Both volumes should be in all collections on orthopedics.

The Kidney: Medical and surgical diseases. By Arthur C. Allen, M.D., pathologist, James Ewing Hospital, assistant attending pathologist, Memorial Cancer Center, New York City, and attending consultant in pathology, Veterans Administration Hospital, Bronx, New York. 4°, cloth, 583 pp., with 1115 illustrations. New York: Grune and Stratton, 1951. $15.00.

This treatise is based on fifteen years' experience in various institutions. The opening chapters treat of embryology, anatomy and physiology and are followed by chapters on uremia, malformations, diseases of the glomeruli and tubules, interstitial nephritis, specific infections, pyelonephritis, renal-pelvic calculi, renal rickets, diseases of vessels, tumors and histologic artefacts. The 339 photographic illustrations are excellent. Lists of selected references are appended to the various chapters. There is an extensive index and the publishing is excellent. The price is reasonable for this type of illustrated book. It should be in all medical libraries.

Veterans Administration Technical Bulletins. Series 10. Volume IV, 1950. 4°, cloth. Washington, D. C.

In this volume are gathered together the medical papers distributed to the staff of the Veterans Administration during 1950. The papers were all prepared by invitation and concern various subjects. There is a timely article on medical planning in atomic warfare. The publishing is excellent, and the volume provides a convenient form for ready reference.

Angewandte und topographische Anatomie: ein Lehrbuch für Studierende und Ärzte. By Prof. Dr. Gian Töndury, ordentlicher Professor der Anatomie an der Universität Zurich. 8°, cloth, 416 pp., with 238 illustrations and 134 tables. Stuttgart: Georg Thieme, 1951. Ganzleinen DM 70./$16.65. Distributed by Grune and Stratton, New York.

This is a new textbook on applied and topographic anatomy. The text is divided into three main divisions: the trunk, including the breast, abdomen, spine and spinal cord; the head and the neck; and the extremities. There is a good index and the publishing is excellent. The color plates are very fine, reminding one of the well known Sobatta atlas. The book should be in all anatomic collections.

Atlas der Hals-, Nasen-, Ohren-Krankheiten: eine Sammlung typischer Krankheitsbilder mit topographischen, diagnostischen und therapeutischen Hinweisen. By Carl von Eicken and A. Schulz von Treeck. Third edition. 4°, cloth, 199 pp., with 470 illustrations. Stuttgart: Georg Thieme, 1951. DM 78. Distributed by Grune and Stratton, New York.

This atlas, first published in 1940, has been revised and brought up to date. A list of old and new anatomic names and a subject index conclude the text. The illustrations are excellent.

Hirnatrophische Prozesse im mittleren Lebensalter: und ihre psychischen Erscheinungsbilder. By Dr. Med. Friedlich W. Bronisch, Privatdozent für Psychiatrie und Neurologie, Wissenschaftl. Assistent an der psychiatrischen und neurologischen Klinik der Universität Heidelberg. 8°, paper, 105 pp., with 43 illustrations. Stuttgart: Georg Thieme, 1951. DM 12.60. Distributed by Grune and Stratton, New York. (Sammlung psychiatrischer und neurologischer Einzeldarstellungen.)

This monograph on atrophic brain processes in middle age with psychic disturbances details 14 cases and discusses similar cases in the literature. A bibliography is appended to the text.

The Pituitary-Adrenocortical Function: ACTH, Cortisone and Related Compounds. A bibliography. Compiled by Karl A. Baer and Marjory Spencer, with the assistance of Paulyne Tureman and Stanley Jablonski. 4°, paper, 366 pp. Washington, D. C.: Army Medical Library, 1950.

This important listing is based to a large extent on the unpublished subject cards of the *Index Catalogue.* The Army Medical Library is to be congratulated on a wise selection of a live subject of timely interest for its first comprehensive bibliography. A total of 3447 titles are listed in various categories, and an author index is provided. Needless to say, the volume should be in all medical libraries.

Memories, Men and Medicine: A history of medicine in Sacramento, California, with biographies of the founders of the Sacramento Society for Medical Improvement and a few contemporaries. By J. Roy Jones, M.D. 8°, cloth, 505 pp., with 33 illustrations. Sacramento: The Sacramento Society for Medical Improvement, 1950. Distributed by Premier Publications, Limited, Sacramento.

In his interesting book Dr. Jones has made a valuable addition to the growing list of local medical histories. The period covered is from the time of the California Gold Rush of 1848 to 1949. A large section of the text is devoted to biographies of prominent physicians of the community. There is a good index.

Reprints from the Oxford Loose-Leaf Medicine: *Purpura and Purpuric States,* by Henry A. Christian, M.D.; *Diabetes Mellitus,* by Alexander Marble, M.D.; *Yaws: Framboesia Tropica,* by George M. Saunders, M.D.; and nine other reprints. 8°, paper. New York: Oxford University Press, Incorporated, 1951.

These reprints are provided to libraries for reference purposes, thereby making it possible to retain in libraries the large volumes of the set.

Physiology of Shock. By Carl J. Wiggers, M.D., Sc.D., professor of physiology and director, Department of Physiology, Western Reserve University School of Medicine. 8°, cloth, 459 pp., with 56 illustrations and 16 tables. New York: The Commonwealth Fund, 1950. $5.00.

In this large book Dr. Wiggers has embodied the results of studies on the peripheral circulation and shock made from July, 1940, to September, 1946. The researches were carried on under the general direction of the author. Dr. Wiggers has also included a critical analysis of the work done else-

where on shock; he reviews the important accumulated experimental and clinical data and assesses the probable validity of the conclusions that have been formulated at various periods. The material is well arranged and the text well written. The chapters, in order, discuss the shock problem as a whole, the clinical signs and symptoms, experimental shock, hemodynamics, mechanisms of peripheral circulatory failure, the heart in shock, respiratory and oxidative functions, metabolic disturbances, toxemic and neurogenic factors and other aspects of the problem.

Each chapter is documented with a list of selected references. An appendix comprises a bibliography of the work of Dr. Wiggers and his co-workers on hemorrhage and shock. There is a good index, and the publishing is excellent. The book is an outstanding contribution to research; it should be in all collections on physiology and surgery.

Chest X-Ray Diagnosis. By Max Ritvo, M.D., assistant professor of radiology, Harvard Medical School, instructor in radiology, Tufts Medical School, roentgenologist-in-chief and director, Department of Radiology, Boston City Hospital, associate radiologist, Beth Israel Hospital, and radiologist, Jewish Memorial Hospital, Jewish Tuberculosis Sanitorium of New England, Revere Memorial Hospital and Hudson Hospital. 4°, cloth, 558 pp., with 615 illustrations. Philadelphia: Lea and Febiger, 1951. $15.00.

This treatise considers the diseases of all the organs of the chest, the bony thorax, the soft tissues of the chest wall and neck and the great vessels. Short bibliographies are scattered throughout the text. The book, essentially an x-ray atlas, is well published and has a good index. It should be in all collections on diagnosis, clinical medicine and roentgenology.

The Scientific Paper: How to prepare it; How to write it. A handbook for students and research workers in all branches of science. By Sam F. Trelease. Second edition. 12°, cloth, 163 pp. Baltimore: The Williams and Wilkins Company, 1951. $2.50.

This valuable literary manual, first published in 1947, has now been published in a second edition, for the use of medical writers.

Fortschritte in der Behandlung schwerer und schwerster Hochspannungsunfälle. By Prof. Dr. Med. H. Fischer and Dr. Med. R. Fröhlicher. 8°, paper, 71 pp., with 23 illustrations. Stuttgart: Georg Thieme, 1951. DM 10.80. Distributed by Grune and Stratton, New York.

This small monograph discusses the progress in treatment of severe high-frequency accidents. The material is based on the author's experimental and clinical experience.

The Postnatal Development of the Human Cerebral Cortex. Volume IV: *The Cortex of the Six-Month Infant.* By J. LeRoy Conel, research associate in pathology, the Children's Medical Center, Boston. 4°, cloth, 177 pp., with 233 illustrations. Cambridge: Harvard University Press, 1951. $12.50.

In the previous monograph of this series the three-month cortex of the infant was described. This volume now considers the six-month cortex; the general pattern of the architectonics was found to be the same as at the age of three months. Changes were found to occur during the intervening three months in each of the nine features of microscopical structure, which are being used in this investigation of developments in the cortex.

Symposium on Steroids in Experimental and Clinical Practice. Edited by Abraham White, M.D., University of California Medical Center, Los Angeles. 8°, cloth, 415 pp., with 103 illustrations and 104 tables. Philadelphia: The Blakiston Company, 1951. $7.50.

This symposium was participated in by a large number of physicians and scientists. Twenty-three papers were presented on the various aspects of the steroids, including their use in various conditions, especially rheumatoid arthritis. Short bibliographies are attached to the various papers. The lack of an index detracts greatly from the reference value of the book. The type and printing are good.

Gynecologic Cancer. By James A. Corscaden, M.D., attending gynecologist, Sloane Hospital for Women, New York. 8°, cloth, 368 pp., with 110 illustrations. New York: Thomas Nelson and Sons, 1951. $6.00.

This new monograph on cancer of the female organs is comprehensive in scope and is based on the author's experience and on extensive knowledge of the pertinent literature. The book is well published; bibliographies are attached to the various chapters. There is a good index, and the book should be in all collections on cancer and on gynecology.

Tumors of the Eye. By Algernon B. Reese, M.D., attending ophthalmologist and pathologist, Institute of Ophthalmology, Presbyterian Hospital, New York, ophthalmologist, Memorial Center for Cancer and Allied Diseases, New York, and clinical professor of ophthalmology, Columbia University College of Physicians and Surgeons. 4°, cloth, 574 pp., with 511 illustrations. New York: Paul B. Hoeber, Incorporated, 1951. $20.00.

In this comprehensive monograph Dr. Reese has described all types of tumors of the eye. The text is divided into 17 chapters, each describing a different class of tumor. A bibliography is appended to each chapter and there is a good index. The publishing is excellent, and the volume should be in all collections on ophthalmology.

Medizinische Toxikologie: Lehrbuch für Ärzte, Apotheker und Chemiker. By Prof. Dr. Phil. et Med. H. Fuhner. Neu bearbeitet von Prof. Dr. Phil., Dr. Med. W. Wirth und Dr. Med. G. Hecht. Third edition. 8°, cloth, 251 pp. Stuttgart: Georg Thieme, 1951. DM 21.60. Distributed by Grune and Stratton, New York.

The first edition of this book was published in 1942. The third edition has been revised and brought to date by Drs. Wirth and Hecht. The material is raranged in a simple manner; it is divided into two main sections — on general toxicology and on poisons and their action. This last section is subdivided into inorganic, organic, plant and animal poisons. The text is well written and the book well published. There is an extensive index of subjects. It should prove valuable for reference purposes.

NOTICES

ANNOUNCEMENTS

Dr. Robert J. Brennan announces the opening of an office for the practice of obstetrics and gynecology at 11 Muzzey Street, Lexington.

Dr. Joseph H. Killelea announces the opening of an office for the practice of internal medicine at 500 Huron Avenue, Cambridge.

ANESTHESIA TEACHING CONFERENCES

The programs of the Anesthesia Teaching Conferences of Boston for the month of January are as follows:

January 7: Physiology of renal circulation, alterations due to hypoxia, obliguria, lower-nephron nephrosis, prerenal azotemia; pharmacology of muscle relaxants; clinical diagnosis, tests and therapy of depressant-drug overdose; case study.

January 11: Physiology of liver; pharmacology of procaine, nupercain, pontocain; postoperative pulmonary complications — etiology, incidence, diagnosis and effects of surgery and anesthesia.

January 21: Normal circulation — regulatory factors, peripheral resistance, cardiac output, venous pressure, effects of anesthesia in surgery; pain-relief methods and indications; case study.

January 28: Physiology of adrenal glands — relation to anesthesia in surgery; pharmacology of sympathomimetics; case report; anesthesia for intra-abdominal surgery.

These teaching conferences are open to the medical public. They are held on Mondays, from 7:00 to 9:00 p.m., in the Stearns Auditorium of the New England Center Hospital, Bennet Street.

THE NEW ENGLAND CARDIOVASCULAR SOCIETY

The next meeting of the New England Cardiovascular Society will be presented by the Peter Bent Brigham Hospital on Monday, January 7, at 8:00 p.m. at the Dorothy Quincy Suite of John Hancock Hall, 180 Berkeley Street, Boston.

PROGRAM

Peter Bent Brigham Hospital (Samuel A. Levine, M.D., presiding)

"The Neurohemodynamics of Acute Pulmonary Edema," by Drs. Stanley J. Sarnoff and Walter T. Goodale (Harvard School of Public Health and Peter Bent Brigham Hospital).

"The Role of the Left Ventricle in Congestive Heart Failure," by Drs. Benjamin Lewis, Florence W. Haynes, Hector Houssay, Richard Gorlin and Lewis Dexter.

"Electrolyte Titration of Digitalis Action. I. Potassium," by Drs. Bernard Lown, John M. Weller, Norman F. Wyatt, Rolf Hoigne, John P. Merrill and Samuel A. Levine.

Invited Papers from New England (Herrman L. Blumgart, M.D., presiding)

"The Routine Use of Quinidine in Acute Myocardial Infarction," by Drs. Frank B. Cutts and Bernard Rapoport, Rhode Island Hospital, Rhode Island.

"Electrical Conductivity of the Peripheral Body Segments," by Dr. Jan Nyboer, Department of Physiological Sciences, Dartmouth Medical School.

"Myocardial Metabolism and Angina Pectoris," by Dr. W. Raab, Bishop De Goesbriand Hospital, Burlington, Vermont.

Interested physicians, medical students and members of the New England Postgraduate Assembly are invited to attend.

BOSTON CITY HOSPITAL HOUSE OFFICERS' ASSOCIATION

The Boston City Hospital House Officers' Association will present the following programs in its Evening Lecture Series for the month of January.

Tuesday evening, January 8 — "Massive Gastrointestinal Hemorrhage," by Dr. Claude E. Welch, associate visiting surgeon, Massachusetts General Hospital. Discussers: Drs. Franz Ingelfinger and Benjamin Alexander.

Thursday, January 10 — "Clinical and Epidemiological Aspects of Coxsackie-Virus Infections," by Dr. Pierre Lepine, head of Department of Virus Research, Pasteur Institute, Paris, France. Discussers: Drs. Alwin M. Pappenheimer and John F. Enders.

Tuesday, January 15 — "Arterial Hypertension: An Evaluation of Some Factors that Influence Its Natural History," by Dr. Eugene B. Ferris, professor of medicine, University of Cincinnati College of Medicine. Discussers: Drs. R. S. Palmer and Robert W. Wilkins.

Tuesday, January 22 — "The Epidemiology of Infectious Hepatitis," by Dr. Richard B. Capps, assistant professor of medicine, Northwestern University School of Medicine. Discussers: Drs. Charles S. Davidson and Charles A. Janeway.

Tuesday, January 29 — "Heart Failure," by Dr. Eugene A. Stead, professor of medicine, Duke University School of Medicine. Discussers: Drs. E. M. Landis and Sidney Burwell.

Thursday, January 31 — "Dicumarol: Its Action on Blood Clotting and Its Clinical Aspects," by Dr. Paul A. Owren, professor of medicine, University of Oslo Medical School, Oslo, Norway. Discussers: Drs. William C. Moloney and Mario Stefanini.

These programs will be held at 7:00 p.m. in the New Cheever Amphitheatre of the Dowling Building of Boston City Hospital.

All interested persons are invited to attend.

THE SPRINGFIELD HOSPITAL

The Educational Program of the Springfield Hospital for the month of January is as follows:

Saturday, January 5.
9–10 a.m. Grand Surgical Rounds.
10–11 a.m. Surgical Conferences in the Staff Conference Room.
11 a.m.–12 m. Combined Medical-Surgical Grand Rounds with Panel Discussion on "The Management of Asthma," with Dr. Oliver J. Menard as moderator and the following as discussers: Medical, Dr. Charles C. Derrick; Allergy, Dr. Bernard H. Tillman; Psychosomatic, Dr. Jerome A. Whitney; and Surgery, Dr. Frederick A. Post. (Staff Conference Room.)

Wednesday, January 9.
11 a.m.–12 m. Psychosomatic Medicine Conference in the Out Patient Department.

Thursday, January 10.
12:15 p.m. Staff Meeting in the Staff Room.

Saturday, January 12.
9–10 a.m. Grand Surgical Rounds.
10–11 a.m. Surgical Conference in the Staff Conference Room.
11 a.m. –12 m. Clinicopathological Conference in the Staff Conference Room.

Tuesday, January 15.
8:30 p.m. Guest Speaker Conference in the Staff Conference Room on "The Purpuras," by Dr. William Dameshek, Director of Blood Research Laboratory at the New England Center Hospital, Boston, and Professor of Medicine, Tufts College Medical School.

Wednesday, January 16.
11 a.m.–12 m. Psychosomatic Medicine Conference in the Out Patient Department.

Saturday, January 19
9–10 a.m. Grand Surgical Rounds.
10–11 a.m. Plastic Surgery Conference in the Staff Conference Room, with Color and Sound Film on "Skin Grafting of Extensive Burns."
11 a.m.–12 m. Medical Death Review in the Staff Conference Room.

Wednesday, January 23.
11 a.m.–12 m. Psychosomatic Medicine Conference in the Out Patient Department.

Saturday, January 26.
9–10 a.m. Grand Surgical Rounds.
10–11 a.m. Pathology Conference in the Staff Conference Room. Dr. William Kaufmann.
11 a.m.–12 m. Surgical Death Review in the Staff Conference Room.

Wednesday, January 30.
11 a.m.–12 m. Psychosomatic Medicine Conference in the Out Patient Department.

SOCIETY MEETINGS AND CONFERENCES

DECEMBER 28 AND JANUARY 4. New England Deaconess Hospital Clinic. Page 548, issue of October 4.
DECEMBER 28. Symposium on Premedical Education. Page 916, issue of December 6.
JANU. 5–30. Springfield Hospital. Notice above.
JANUARY 5, FEBRUARY 2, MARCH 1, APRIL 5 AND MAY 3. New England Society of Anesthesiologists. Post Graduate Education Course. Page 996.
JANUARY 7. New England Cardiovascular Society. Notice above.
JANUARY 7, 11, 21, 28. Anesthesia Teaching Conference. Page 1031.
JANUARY 7, FEBRUARY 25 AND APRIL 15. Massachusetts Society for Research in Psychiatry. Page 792, issue of November 15.
JANUARY 8. New England Society of Anesthesiologists. Page 996, issue of December 20.
JANUARY 8–31. Boston City Hospital House Officers' Association. Notice above.
JANUARY 9. Essex North District Medical Society. Page 996, issue of December 20.
JANUARY 10. Tufts Medical Alumni Lecture. Page 996, issue of December 20.
JANUARY 10. The Recognition and Management of Common Kidney Diseases. Dr. Robert P. McCombs. Pentucket Association of Physicians. 8:30 p.m. Haverhill.

(*Notices concluded on page xi*)

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